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American Journal of Clinical Pathology

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PROSPECT AND RETROSPECT*

H. J. CORPER

National Jewish Hospital, Denver, Colorado

In filling this most signal position this evening, I have only one regret and that is that this pleasure could not have been enjoyed by my colleague and friend who sacrificed so much in time and effort to establish this Society for a cause he sincerely believed in. During the infancy of this Society the rest of us proved only counselors and team mates and I am certain I voice the opinion of all who were fortunate enough to have played any part in that august occasion, the birth of The American Society of Clinical Pathologists, almost a decade ago, in the Missouri Baptist Hospital on May 22, 1922, at 8:00 p.m. I hope we shall never cease to pay tribute to the sacrifices of Ward Burdick for the welfare of the practicing clinical pathologist.

Dr. Burdick frequently reminisced about that first meeting attended by about forty men and a few ladies; very few of those present were personally acquainted with one another when Dr. George Ives of St. Louis called the assemblage to order for the "first successful national meeting of clinical pathologists," but the parting at the close of the meeting found East and West, North and South as friends united in one worthy effort—a ship embarked on an important voyage with able officers and committees in charge. It is hardly fitting to review names as they are all well known to you and I might be accused of the error of willful omission which, I assure you, should make me regretful. However, in retrospect I choose this course, risking possible criticism, to refresh your memory historically speaking and to satisfy a personal pride in the accomplishments of my friends and colleagues.

* Presidential Address read before the Eleventh Annual Convention of the American Society of Clinical Pathologists, New Orleans, Louisiana, May 6–9, 1932.

There were many hours of arduous labor on the part of the founders such as our first president Dr. Philip Hillkowitz and the early members. Colorado and Texas were preeminent in the early history because they had existing state societies of clinical pathologists which acted as the impetus for the national organization. It was Dr. Burdick's hope that some day every state would have a society like that in Colorado.

Dr. William Carpenter MacCarty of Rochester, Minnesota, proposed the appointment of a committee of five to carry out the purpose of that first day of the convention in St. Louis the founding of the society, and to submit a Constitution and By-Laws for consideration. The next morning saw such a Constitution prepared and an extemporaneous scientific session from the talent present was ready for the afternoon gathering. The number of charter members at the close of the first annual convention was 145.

The Second Annual Convention, June 25–26, 1923, was held in conjunction with the San Francisco meeting of The American Medical Association and in spite of the distance, more than seventy members registered.

About this time the organization accepted The Journal of Laboratory and Clinical Medicine as the official organ for its transactions which prior to this had been sent out in pamphlet form. Dr. MacCarty pointed out that the chief object of the Society was active coöperation or for the interest and mutual benefit of its members. He stated that the formation of the Society was stimulated by: (1) The necessity of picking out the practical diagnostic and therapeutic laboratory facts and methods from those of pure scientific interest; (2) the necessity of standardization of these facts and methods; (3) the necessity of setting a standard educational requirement for laboratory consultants to obviate the rapid increase of false claims of technicians who frequently conduct commercial laboratories, the value of which many physicians are unable to determine; (4) the necessity of maintaining laboratory sciences within the realm of the profession of medicine and not allowing them to become merely commercial adjuncts; (5) the stimulation of the interest of the

general profession in the real value of the laboratory in the practice of medicine and surgery; (6) needed assistance in the standardization of hospitals.

The Third Annual Convention was held in Rochester, Minnesota, June 6 and 7, 1924. The members were treated to the hospitality of The Mayo Clinic and its members, and at this meeting business matters and economic topics were relegated more or less to the background while science held sway. Round Table discussions were initiated to the delight and illumination of all present. At this time Dr. William J. Mayo and Dr. Malcolm T. McEachern paid tribute to the clinical pathologist's efforts. More than fifty applicants for membership were voted on favorably at the business session of the Convention. A symposium was held on the standardization of laboratory procedures.

In the transactions of the meeting under "News and Notes," we find that

"The American Society of Clinical Pathologists, however, is a young, vigorous and actively growing organization with strong proliferative tendencies aiming to keep the members constantly in touch with one another and spurring them on to better scientific and technical perfection of their specialty. The clinical pathologist is in the best strategic position to promote the success of the hospital standardization program. The American College of Surgeons recognizing the important rôle played by the hospital pathologist has been in close touch with and has actively coöperated with the American Society of Clinical Pathologists in their common endeavor to raise the medical level of the hospitals of this continent. At the section meetings arranged by the college in various parts of the United States a clinical pathologist has been placed on the program to discuss the problem of the laboratory."

Then follow notes on the competent supervision of hospital laboratories and a survey of hospital laboratories.

The Fourth Annual Convention was held in the ball room of the Benjamin Franklin Hotel at Philadelphia on May 20–23, 1925, with Dr. John A. Kolmer presiding. A feature of this meeting was a report on laboratory standardization which was discussed by Dr. Ruth Gilbert of New York and Dr. M. P. Colwell of The American Medical Association.

A pertinent suggestion at this meeting was a report from the Committee on Publication that the Society was considering pub-

lishing its own journal but that this was not deemed advisable for the present, and we heard for the first time that the Society had established a Service Bureau. The matter of registration of the technicians was considered of sufficient importance to be referred to the Executive Committee. At this time public health, state, city and county laboratories also came up for discussion and Dr. Sondern, upon accepting the presidency, pledged himself to solve the problem "as best we can."

A special feature of the Philadelphia meeting was the initiation of a commercial and scientific exhibit which proved such an outstanding success, both for the members and exhibitors, that it was considered advisable to continue this.

Notable also was the valid objection to considering "a clinical pathologist as a manipulator of fixtures and inanimate substances." As outlined by Dr. Herman Spitz, "a clinical pathologist must be a physician, primarily and basically," and "clinical pathology is the science of interpreting morbid processes as determined by means of various laboratory aids and correlating them with clinical symptoms."

With the news that the Fifth Annual Convention, in 1926, was to be held in Dallas, Texas, on April 15–17, there was great rejoicing because from Texas, as one of the pioneer states, originated the idea of the national society. The names of Drs. Moursund and Black will always remind those present of a great time.

With this came the valuable suggestion of the Past-President, Dr. John A. Kolmer, for an official text on "Approved Laboratory Methods in Clinical Pathology." It is rather singular that a Research Committee should have been appointed at this time by the President to investigate the question, and study the advisability of publishing the book of approved methods suggested by Dr. Kolmer.

The awarding of a prize to stimulate original research and an official publication of the Society were discussed at this time.

Illness prevented the Secretary-Treasurer, Dr. Ward Burdick, from attending the meeting but his energetic efforts were evident in the smooth conduct of the affairs.

The Sixth Annual Convention held in Washington, D. C., May

13–16, 1927, saw close coöperation with the American College of Surgeons in raising to the highest level all laboratories and standardized hospitals. The laity had become educated to the important rôle the pathologist plays in the team work of the hospital. Here for the first time we heard a report from the Committees on Research and a report by Dr. Kano Ikeda on the Registration of Technicians, features of the Society which have now assumed important proportions.

The meeting convened under Dr. William G. Exton and notable among the guest speakers were Dr. George K. Burgess, Director of the Bureau of Standards, Dr. George W. McCoy, Director of the U. S. Hygienic Laboratories, Washington, D. C. and Rear-Admiral E. R. Stitt.

Following the report of the Publication Committee by Dr. Kolmer, it was suggested that the Committee appoint the editors and associate editors and that work be begun at once on the new book on clinical pathology.

The Seventh Annual Convention greeted the members in Minneapolis, June 8–11, 1928 with Dr. A. H. Sanford in the Chair. The Society mourned the untimely demise of the Secretary, Dr. Ward Burdick, but his inspiration made all feel that he was still carrying on. Companionship was the keynote of this meeting under the excellent arrangements of the local committee headed by Dr. Charles R. Drake. The scientific and commercial exhibits proved a valuable asset due to the untiring efforts of Dr. A. C. Broders and Dr. Kano Ikeda.

To pave the way for possible future expansion and publication of a Society journal, the dues at this time were increased to a maximum of $10.00. Also a notable feature of this meeting, aside from the excellent scientific program, was the paper by Dr. William O'Brien on "The Cults." Another important feature of this meeting was a discussion on associate membership and their ethics. In addition an endorsement of the efforts of approving of laboratories by the American Medical Association was favored.

The Research Committee recommended the establishing of a yearly "Ward Burdick Research Award."

During this meeting also a most laudable innovation was initi-

ated by Drs. Charles Sheard and A. H. Sanford "for turning over to the American Society of Clinical Pathologists the privilege of exercising control over the commercial production of their new instrument for hemoglobin determinations."

At this time Dr. A. H. Schade suggested a revision of the application blank for membership which was subsequently executed.

In the February, 1929 number of The Journal of Laboratory and Clinical Medicine we note a proposed working scheme of the Registry of Technicians including the objects, the Board of Registry, the classification of laboratory technicians, the registration of schools for laboratory technicians, a placement bureau, and a code of ethics, and are advised that this Registry is now functioning quite satisfactorily and that technicians are rapidly availing themselves of the opportunity to obtain certificates.

In the March, 1929 number we are advised of the establishment of a "Ward Burdick Research Award" of the American Society of Clinical Pathologists dedicated to a man who was never too busy to answer a call on behalf of the Society. The award consisted of an appropriate gold medal bearing the profile likeness of Dr. Ward Burdick, and the nature of the award on its face, and on the reverse side the seal of the Society, a laurel wreath, and a place for the name of the recipient and the date of presentation.

The Eighth Annual Convention of the American Society of Clinical Pathologists was held in Portland, Oregon, July 5–8, 1929 with Dr. F. W. Hartman in the Chair. Drs. H. H. Foskett and C. H. Manlove will always be remembered for their excellent arrangements and western hospitality. It had been the custom throughout these years to hold the meetings and banquets in the headquarters hotels. This offered the unusual opportunity for fraternizing which always proved delightful and carried fond remembrances of friendship.

At this meeting for the first time the "Ward Burdick Medal" was presented to Dr. Walter M. Simpson of Dayton, Ohio for investigations in tularemia.

In 1929, we note the custom of official representation with other societies which was well exemplified in the presence of five representatives at the 19th Clinical Congress of the American College of Surgeons at Chicago, October 14–18, 1929, and two representa-

tives at the 58th Annual Convention of the American Public Health Association in Minneapolis, September 30 to October 5, 1929.

At the Portland meeting we learned that the text on Clinical Pathology was progressing rapidly and that the publication of a Journal by the Society was being further pursued.

The Committee on Exhibits by Dr. C. H. Manlove had presented eight exhibits, a laudable showing, and at this meeting the Board of Registry was officially acknowledged in the Constitution.

In 1930, we were advised that the scientific exhibits had assumed such proportions under the able supervision of Dr. C. I. Owen of Detroit, that two prizes, a gold and a silver medal were to be awarded.

The Ninth Annual Convention was held in Detroit on June 20–23, 1930, under the able leadership of Dr. J. H. Black of Dallas, Texas. A special feature of this meeting was a visit to Parke-Davis and Company under the kindly guidance of one of our Fellows, Dr. Walter E. King.

At this meeting the names of Dr. William H. Welch, Rear-Admiral E. R. Stitt, and Dr. Louis B. Wilson were proposed for honorary membership.

The Publication Committee reported that the book on Clinical Pathology would be ready for publication next year. The first awards for scientific exhibits were made, the gold medal being presented to Dr. E. R. Mugrage and Dr. Rodney H. Jones, and the second award to Dr. T. J. Curphey.

The Executive Committee at a post-meeting session June 23, 1930, authorized Dr. John A. Kolmer to negotiate with The Williams & Wilkins Company for the publication of the Society's journal and the first number appeared in January, 1931, under the editorship of Dr. T. B. Magath and an associate editorial staff of Fellows of the Society.

An interesting side-light of the activities of the Society is the discussion of the subject of the training of lay technicians by Dr. Walter E. King before the Congress of Medical Education, Medical Licensure and Hospitals, in February, 1930, fulfilling an important function of the Society. Dr. King pointed out the importance of specifying the minimum of work for students and of classifying technicians.

The Tenth Annual Convention was held in Philadelphia, June 7–9, 1931, under the Chairmanship of Dr. Kenneth M. Lynch. One of the interesting features of this meeting was the privilege to visit the little old brick building in which Osler performed his autopsies and to see his autopsy table and examine his original protocols. At this meeting the Editor advised the Society that a contract had been entered into with The Williams & Wilkins Company for the publication of the AMERICAN JOURNAL OF CLINICAL PATHOLOGY, and that three issues were off the press, and that the JOURNAL was to appear at bimonthly intervals.

As was noticed earlier, the success of the Society was assured as the result of the magnetic personality of its founders and leaders, and the untiring and unceasing effort on their part. At the close of the First Annual Convention in 1922 the number of charter members totaled 145. In 1926, the roster showed a membership of 350, while the 1928–1929 roster showed a membership of 380. At the Philadelphia meeting, in 1931, the Secretary reported 376 active members of the Society: a steady increase showing healthy growth of the Society from 1922 to 1930 in spite of the loss of members each year by deaths and by discontinuing practice. I am now advised by Dr. Giordano that our total membership for this year is 358, a decided drop from last year, and of these sixty-seven are in arrears for one year, eighteen for two years and thirteen have been dropped for non-payment of dues and five have resigned.

In retrospect we can hardly fail to feel that the Society has made remarkable progress in welding the friendships of the clinical pathologists, and that through the efforts of the Society the status of the clinical pathologist has been decidedly elevated in the eyes of his medical colleagues and in the minds of his lay friends including hospital executives and executive boards. It would, however, be unfair to expect that the work is completed and that the problems facing the clinical pathologists are insignificant. If ever there was a need for the Society such need becomes even more pertinent today. A work well initiated that must continue and be elaborated upon. It is with this thought that I chose to close my address to you, my colleagues, in prospect.

With your kind permission, I should like to prospect with a view to benefiting not only ourselves but also our friends the patients and colleagues in allied fields. To do this efficiently I feel that we should be willing to do honor to Fellows in our own midst who merit such honors for industry and accomplishment, and in addition we should not hesitate to pay warranted honor to our scientific friends in other branches of endeavors. And to this end we have invited guests to join us at our annual meetings and we have seen fit to present to our own Fellows appropriate awards, one dedicated to perpetuating the name of one who insured the early success of the Society by personal sacrifice and the instillation of ideals. During this year, your President, inspired by the request of some of our best Fellows took upon himself the responsibility of appointing a number of new committees, one of them being for the purpose of doing honor to some international figure who has contributed to the welfare of clinical pathology, and the Society by card ballot approved the unanimous recommendation of the committee by a 4 to 1 majority. It is hoped by the Award Committee and concurred in by your President, that this may be perpetuated by the Society until the problems of clinical pathology have disappeared. In line with the general policy previously executed by the Society, it is hoped that succeeding presidents will see fit to perpetuate some of the committees appointed this year by your President to assist in sponsoring friendships with other scientific groups. Needless to say, some of them may cease to function and will become automatically obsolete and should then be discontinued. If I may plead for my successors in this Chair, may I suggest that they be given every opportunity to appoint such new committees as they may consider of value to them during their period of office. Such power is automatically given the president in other distinguished societies and should be our generous attitude toward our presidents. It has become a pleasure to other societies to seek our coöperation and friendship and may I suggest that we encourage this by appearing on their programs and by presenting exhibits and demonstrations as representatives of the American Society of Clinical Pathologists.

It is with pleasure that I, as a Fellow of this Society, look for-

ward to an International Union of Clinical Pathologists. You will recollect we made the Secretary of the British Association a Corresponding Member of our Society, 1929, and in 1930 we initiated an Honorary Membership. Needless to say, that the aforesaid functions are represented by committees of our Society which I hope my successor will continue—The Research Committee, The International Award Committee, The Committee for Honorary Membership, The Committee on Necropsies, and The Committee on Exhibits to Hospital and Medical Associations. Permit me also to express my appreciation of the excellent work of our Registry of Technicians.

I cannot dwell long upon my hopes for the Society as such in prospect but feel that an expression of opinion based on my personal experiences and my hopes for the Society may prove of some value to the membership. If we are to abide strictly by our Constitution and By-Laws, I believe they need careful consideration and revision by a group of qualified Fellows and I should advise leniency but thoughtful wording in such revision. I believe the Society has reached a point where the offices of Secretary and Treasurer should be separated and that small annual expenditures should be within the discretion of these two officers while large expenditures exceeding say one hundred dollars for an individual purchase should be approved by the Society.

The Registry of Technicians is a separate department of the Society and should be treated as such and should not be under the Secretary.

And finally, after a complete and satisfactory revision of the Constitution and By-Laws, it might be well to have a Society Parliamentarian who without prejudices or biases can with fairness render parliamentary decisions when requested. In closing, I would request also that unanimous decisions when rendered by committees be given serious and favorable consideration by the Executive Committee when called upon for their decision.

I look forward to another decade of accomplishment and to a bigger and better American Society of Clinical Pathologists, actively participating in the functions of an International Association of Clinical Pathologists.

THE DEMONSTRATION OF MYCOBACTERIUM TUBERCULOSIS IN EXUDATES, TISSUES, AND BODY FLUIDS: CONCERNING GUINEA-PIG INOCULATION AND CULTURAL METHOD FOR THE DEMONSTRATION OF MYCOBACTERIUM TUBERCULOSIS

W. W. HERRMANN, G. H. HANSMANN, AND THELMA DECAPITO

(From the Departments of Pathology and Bacteriology, and Hygiene and Preventive Medicine of the State University of Iowa, Iowa City)

Because of the protean features of the lesions produced by, and the widespread distribution of, *Mycobacterium tuberculosis*, the physician is frequently called upon to make examinations for the establishment of the diagnosis of tuberculosis. No greater service can be offered a patient and those closely associated with him than an accurate diagnosis of tuberculosis. No greater injustice can be done to an individual than erroneously to brand him as tuberculous when such a false diagnosis could have been obviated. It is apparent that when a diagnosis of tuberculosis is under consideration methods of examination are still inaccurate. Any method which may increase accuracy in diagnosing tuberculosis should be given thorough and sympathetic attention.

The safest ground upon which a diagnosis of tuberculosis may rest is the recovery and identification of the etiological agent from the suspected lesion. One of the simplest methods, and hence the one most widely used, is the examination of a smear from the lesion stained immediately by one of the acid-fast methods. Pottenger demonstrated that this method is inadequate in many cases, since upwards of 100,000 organisms must be present per cubic centimeter of material in order that they may be consistently found in smears.

The laboratory worker is always on the alert for a more delicate method with which he may improve his armamentarium for the demonstration of *Mycobacterium tuberculosis*. According to

Feldman and Magath,[7] as early as 1867, even before the discovery of the organism by Koch, Marcet, advocated the use of guinea-pigs for the purpose of demonstrating the tuberculous nature of material from suspected cases of tuberculosis in man. This animal is highly susceptible to infection with the *Mycobacterium tuberculosis*, fifty organisms, according to Webb, Gilbert, and Havens,[13] being sufficient to set up systemic lesions of the disease. In addition, the guinea-pig is able to overcome a moderate number of contaminating organisms which may be inadvertently present in the inoculum. Guinea-pigs are readily available, have been demonstrated by Magath and Feldman to be the basis for a most reliable method of demonstrating the presence of *Mycobacterium tuberculosis* when present in small numbers, and therefore inoculation of guinea-pigs is the test most widely used in laboratories.

Among the objections to guinea-pig inoculation are the length of time (six to eight weeks) which must elapse before the typical lesions develop, the initial cost of the animals, and cost of maintenance during the time that lesions are developing, and a certain amount of danger of the animal's dying from intercurrent infection. The time elapsing before a positive report may be returned is shortened, it is true, if local lymph-nodes are found to be enlarged and are removed for examination without sacrificing the animal. This procedure entails considerable time, however, as compared with the examination of a tube of culture medium. Then, too, the questions although not very important as to whether some guinea-pigs may not be resistant to infection or, on the other hand, develop spontaneous tuberculosis, always enter into a discussion of the guinea-pig method.

The cultivation of *Mycobacterium tuberculosis* on artificial mediums followed almost immediately the discovery of the organism. Pawlowsky[10] pointed out the usefulness of potato medium soon after Koch's discovery. Dorset later showed that eggs contained the food requirements for the cultivation of *Mycobacterium tuberculosis* and later Petroff[11] added a bacteriostatic dye to Dorset's[5] medium in order to inhibit the growth of contaminants. Within the last few years many other formulas for the

preparation of mediums suitable for the growth of these organisms have been proposed. It was not the purpose of this study to compare of the relative efficacy of these various mediums in cultivation of *Mycobacterium tuberculosis* from suspected material, but rather to select one such medium, which had shown promising results, and subject it to prolonged parallel study with guinea-pig inoculation which was in use in this laboratory, for the routine demonstration of the *Mycobacterium tuberculosis* in tissues, exudates, and body fluids.

The study was begun early in 1930 and an attempt was made, as far as practicable, to use consecutive materials as they were submitted to the hospital laboratory for examination with reference to the presence of *Mycobacterium tuberculosis*. Where the material submitted was so meager that it appeared the guinea-pig test would be invalidated by dividing it, only the guinea pig was inoculated. Because of a changing personnel in the bacteriological laboratory, otherwise available material was discarded without being cultured. However, up to July 1, 1931, 527 parallel attempts had been made to recover the *Mycobacterium tuberculosis* by guinea-pig inoculation and by culture.

PROCEDURE

The culture medium selected was the crystal-violet, potato-slant preparation described by Corper and Uyei. At first the inoculum was treated with 6 per cent sulphuric acid before seeding, but later, when the authors reported more favorable results with 5 per cent oxalic acid, the latter method of inhibiting the growth of contaminating organisms was used. The cultures were made by one of us (T. D.), in the State Bacteriological Laboratory, three tubes being seeded with each specimen after being treated in the prescribed manner. Fluids were centrifugalized before treatment and the solid specimens were triturated with a sterile mortar and pestle. At first the seeding was done with a loop. Later it was felt that a quantity of inoculum, more comparable to that received by the guinea-pig would be used, if the seeding were done with a sterile pipette which permitted the inoculation of several drops of the centrifugalized specimen, and that modification was used thereafter. Cultures were observed weekly and, unless growth appeared, were under observation for a total of twelve weeks. The culture was considered to be positive if the characteristic, dry, yellow, granular, piled-up colony developed, which, when smeared out and stained, was proved to be composed of acid-fast, bacillary organisms.

The guinea-pigs were inoculated subcutaneously near the groin. Fluids were injected by means of a syringe and hypodermic needle, while solid material was inserted through a small skin incision which was then closed by suture. Usually only one guinea-pig was used for each specimen. These animals were then kept in small cages in the animal room, not more than four and usually two or three animals to a cage. All animals were sacrificed at the end of six weeks if they had not died before that time. Post-mortem examinations were made of all guinea-pigs as soon after death as possible. The usual evidences of tuberculosis are a local, dirty, weeping ulcer at the site of inoculation, enlarged, inflamed and sometimes caseous lymph-nodes draining the site of inoculation, and an

TABLE 1

COMPARISON OF GUINEA-PIG INOCULATIONS AND CULTURES

	TISSUE	URINE (URETERAL)	URINE (VOIDED)	URINE (BLADDER)	EXUDATE	SPINAL FLUID	SPUTUM	STOOL	GASTRIC CONTENT	CYST FLUID	TOTAL
Guinea-pig negative, culture negative.....	48	202	10	10	70	15	5	2		1	363
Guinea-pig positive, culture positive.....	15	17	2		10	3			1		48
Guinea-pig positive, culture negative.....	9	4			11	3			1		28
Guinea-pig positive, culture incomplete...		2		1	1						4
Guinea-pig negative, culture positive.....	3	2	1		1						7
Guinea-pig incomplete, culture positive...	4				1						5
Guinea-pig negative, culture incomplete..	2	13		2	5		1				23
Guinea-pig incomplete, culture negative..	9	20		3	8		3				43
Guinea-pig incomplete, culture incomplete.....	1	1	2		1					1	6
Total.....	91	261	15	16	108	21	9	2	2	2	527

enlarged spleen which contains many small, white, discrete, somewhat firm tubercles. A guinea-pig was considered positive if it exhibited one or more of these gross findings from which typical acid-fast rods could be demonstrated by direct smear and stain.

COMMENT

Table 1 indicates the source and character of the various materials used and the results obtained. In 411 instances there was perfect agreement between the guinea-pig inoculation and culture, 363 negative tests and forty-eight positive tests. There were thirty-five instances of disagreement; twenty-eight instances in which the guinea-pig was positive but no growth

appeared in the culture tube, and seven instances in which there was a typical growth on the culture medium but no lesions could be demonstrated in the animals. In six of these seven instances, the organism recovered by culture was injected into guinea-pigs and produced typical tuberculous lesions containing acid-fast bacilli. In the other instance, the culture was no longer available for an animal pathogenicity experiment. There was no clinical evidence of tuberculosis in the urinary tract of this patient, the specimen being ureteral urine obtained by catheter, and no further organisms were isolated on repeated attempts. In all, six guinea-pigs and six sets of cultures were made from catheterized ureteral urines of this patient.

Eighty-one of the 527 tests were incomplete in that either the culture tubes or guinea-pigs or both could not be properly evaluated. The chief reason for failure with the guinea-pig test was death of the animal shortly after inoculation and before tuberculous lesions had time to develop. Death was presumably due to infection with other organisms in the inoculum and occurred usually within seventy-two hours. The causes of failure with the cultures were equally divided between contamination, loss by breakage in the centrifuge, and prolonged treatment with acid. The work was carried on in the midst of a heavy routine so that in a few instances the material was subjected to contact with acid for a longer period of time than that recommended by Corper and Uyei.[2,3] It is doubtful, from the experience of Woolsey,[14] if this prolonged acid treatment had any effect on the *Mycobacterium tuberculosis*, but such cultures were classed as incomplete.

Thus, considering only the positive reports in which both tests were complete, the guinea-pig method surpasses without question, the culture method. If, however, the negative findings and the incomplete tests are included, even though they may be of doubtful clinical value, the two methods more nearly balance, the guinea-pig tests being incomplete in fifty-four instances, whereas the culture results were incomplete in thirty-three.

Hohn[8] believes that the question is not so much which of the two methods, culture or animal inoculation, is the superior, but rather, which type of material should be cultured and which

inoculated into a guinea-pig. We had this point in mind when we began our comparison. A study of the table fails to show any particular type of material which gives decidedly better results with one method than with the other. There are instances in each of the major brackets in which either of the methods was positive in the face of a negative test by the other method.

Among the 363 instances in which both tests were completed with a negative result, there were twenty-two clinical cases in which the diagnosis of tuberculosis had been made with respect to the lesion in question, in spite of the inability to demonstrate the organism. In two of these cases the diagnosis was subsequently substantiated by the demonstration of *Mycobacterium tuberculosis*.

Hohn,[8] Corper,[1] and Corper and Uyei,[4] each with the method developed in his own laboratory, report results equal or superior to the guinea-pig inoculation in the recovery and the identification of *Mycobacterium tuberculosis* from suspected materials. Woolsey, using Herrold's medium, finds agreement in 93 per cent of 130 cases and superiority of the medium over the animal in five of the nine cases of disagreement. Feldman,[6] Stadnichenko and Sweany,[12] and Lutz,[9] using various mediums including Hohn's and Corper's, on the other hand, consider the animal inoculation to be superior to cultural methods. This, too, is the position that we take at this stage of the study. We believe that cultural methods have a definite place in the laboratory diagnosis of tuberculosis and the demonstration of the organism. As the table indicates, there are eleven instances, leaving out the one doubtful case, in which *Mycobacterium tuberculosis* was demonstrated to be present in material by means of the culture tube, in which the guinea-pig either died before the disease developed or else was negative when examined for tuberculosis at the end of six weeks. On the other hand there are so many instances in which the guinea-pig method surpassed the cultural method, that we believe it to be the superior method as a routine procedure. The series is being continued in an attempt to improve our technique, hoping to approach the favorable results reported by Corper and Uyei[2] and others.

CONCLUSIONS

1. Five hundred and twenty-seven parallel animal inoculations and cultures have been carried out to demonstrate the *Mycobacterium tuberculosis* in tissues, exudates, and body fluids.

2. Guinea-pig inoculation has surpassed the cultural method for the demonstration of *Mycobacterium tuberculosis* in our series.

3. Guinea-pig inoculation surpassed the cultural method for all types of inoculum.

4. The cultural tests showed the greater percentage of endeavors carried to completion.

5. Approximately 10 per cent of the patients who presented the clinical signs of tuberculosis and from whom the initial material from the suspected tuberculous lesion was negative for *Mycobacterium tuberculosis* by both methods, have, on subsequent employment of the same methods, been proved tuberculous.

6. The cultural method is a good supplementary method to use in conjunction with animal inoculation for the recovery of *Mycobacterium tuberculosis* from routine suspected materials.

REFERENCES

(1) Corper, H. J.: The certified diagnosis of tuberculosis. Jour. Am. Med. Assn., **91:** 371–374. 1928.

(2) Corper, H. J., and Uyei, Nao: The cultivation of tubercle bacilli. An improved method for isolation from tuberculous materials. Jour. Lab. and Clin. Med., **13:** 469–480. 1928.

(3) Corper, H. J., and Uyei, Nao: Oxalic acid as a reagent for isolating tubercle bacilli and a study of the growth of acid-fast nonpathogens on different mediums with their reaction to chemical reagents. Jour. Lab. and Clin. Med., **15:** 348–369. 1930.

(4) Corper, H. J., and Uyei, Nao: Further observations with a new method for cultivating tubercle bacilli. A comparison with guinea-pig inoculation and Petroff's method. Jour. Lab. and Clin. Med., **14:** 393–412. 1929.

(5) Dorset, M.: The use of eggs as a medium for the cultivation of bacillus tuberculosis. Am. Med., **3:** 555–556. 1902.

(6) Feldman, Wm. H.: A comparison of different culture methods for the isolation and growth of Mycobacterium tuberculosis. Am. Jour. Clin. Path., **1:** 285–302. 1931.

(7) Feldman, Wm. H., and Magath, Thomas B.: The reliability of guinea-pig inoculation in the diagnosis of tuberculosis. Am. Rev. Tuberc., **24:** 312–325. 1931.

(8) Hohn, Joseph: Vier Jahre Kultur des Tuberkelbazillus zur Diagnose der Tuberkulose. Zentralbl. f. Bakteriol., **113:** 366–376. 1929.

(9) Lutz, G.: Zur Frage: Tierversuch oder Kultur zum Nackweis von Tuberkulose. Zentralbl. f. Bakteriol., **114:** 232–238. 1929.

(10) Pawlowski, A. D.: Culture des bacilles de la tuberculose sur la pomme de terre. Ann. de l'Inst. Past. Par., **2:** 303–308. 1888.

(11) Petroff, S. A.: A new and rapid method for isolation and cultivation of tubercle bacilli directly from the sputum and feces. Jour. Exp. Med., **21:** 38–42. 1915.

(12) Stadnichenko, Asya, and Sweany, H. C.: A comparison of culture and animal inoculation of sputum in the diagnosis of tuberculosis. Am. Jour. Clin. Path., **1:** 303–313. 1931.

(13) Webb, Gerald B., Gilbert, Geo. B., and Havens, Leon C.: Blood-platelets and tuberculosis. Arch. Int. Med., **14:** 743–756. 1914.

(14) Woolsey, C. I.: The diagnosis of tuberculosis. Jour. Inf. Dis., **49:** 177–182. 1931.

CHEMICAL AND BACTERIOLOGICAL STUDIES OF PYRIDIUM

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In the biochemical investigation of pyridium which we conducted, the first series of our bacteriologic tests were made to determine the antibacterial value in vitro of the product on *Escherichia coli* (B. coli), *Staphylococcus aureus*, Streptococcus (Gay), *Corynebacterium diphtheriae* and Pneumococcus.

Pyridium was chosen as representative of the azo dye group as it appeared to be chemically stable and definitely antibacterial in vitro. In a previously published report,[1] we showed that pyridium had definite bacteriostatic properties in concentrations of 1:4,000 to 1:10,000, the average being about 1:8,000, against *Esch. coli*, *Staphylococcus aureus*, *Corynebacterium diphtheriae*, Pneumococcus (Gay), and Streptococcus. The bacteriostatic properties were not inhibited to any marked degree by the addition of such biological fluids as urine and blood serum, when added to the mixtures of pyridium and organisms. The compound showed bactericidal properties for the test organisms in concentrations of 1:4,000 to 1:10,000 with an average of 1:5,000.

In view of these findings it was deemed advisable to test the bactericidal and bacteriostatic properties of pyridium in vivo, by investigating the urine excreted by individuals who were given varying doses of the dye. The report includes (a) measurements of the dye excreted by the evaporation and precipitation method, the colorimetric method and the concentration as based on a color index ratio, and (b) bacteriologic studies including control experiments, determination of the effect of pyridium on a series of urine specimens obtained from twenty-seven individuals, each taking 0.6 gram of pyridium per day and also on a series of urine specimens obtained from individuals taking 0.9

gram per day in three doses of 0.3 gram each, and on catheterized specimens from patients taking 0.6 gram per day. The specimens were inoculated with staphylococci and *Esch. coli.*

EXPERIMENTAL

Total dye excreted

The first series of experiments were intended to show the concentrations of dye excreted in the urine obtained from individuals who were taking six 0.1 gram tablets of pyridium daily. The tests were carried out over a period of seventy-two hours in the case of each individual. The total volume of urine for each day was measured and the dye content determined according to the following technique.

A. Evaporation and precipitation method. The total urine in each case was placed in large shallow porcelain dishes and evaporated to about one-tenth of the original volume by heating on an asbestos mat placed over an electric plate. The temperature was never raised above 30 to 35°C. In order to facilitate evaporation a current of air was drawn over the surface of the liquid. The rapid evaporation which resulted from this method also helped to keep the temperature low. The concentrated urine was then acidified with dilute hydrochloric acid and cooled for twenty-four hours by immersing the dish in cracked ice. The precipitate was collected on a weighed filter paper and washed with distilled water containing a few drops of hydrochloric acid and then washed with distilled water, dried in a desiccator and weighed.

Table 1 gives the total volume of urine (average, 994.5 cc.) excreted by each individual while taking 0.6 gram of pyridium per day, the total volume of liquid was restricted as much as possible in each case.

Table 2 records the daily excretion of pyridium as determined by the evaporation and precipitation method.

B. Total volume in seventy-two-hour period. Because of the rather low percentage of recovery of pyridium, a second series of experiments was conducted in which the total volume for a seventy-two-hour period was collected and evaporated according to the method used in the preceding series.

This method gives rather variable results apparently due to the fact that the pH of the precipitating mixture cannot be accu-

rately controlled. This is evident from the results recorded in table 2, where the percentages of recovery ranged from 12.7 to 56.1 with an average of 29.2. In the case of the second series where the urine was collected during a seventy-two-hour period the range of recovery of pyridium was from 32.47 to 44.05 per cent with an average of 36.25. The higher percentage of recovery in the second series is apparently due to the greater concentration of pyridium in the evaporated residue from a seventy-two-hour

TABLE 1

AVERAGE DAILY VOLUMES OF URINE EXCRETED IN TEN PATIENTS

FIRST DAY	SECOND DAY	THIRD DAY
1,001.5 cc.	1,059.5 cc.	921.5 cc.

TABLE 2

AVERAGE DAILY EXCRETION OF PYRIDIUM IN TEN PATIENTS

FIRST DAY	SECOND DAY	THIRD DAY	PERCENTAGE RECOVERED
140.7 mgm.	181.35 mgm.	183.1 mgm.	29.2

TABLE 3

AVERAGE EXCRETIONS OF PYRIDIUM DURING A SEVENTY-TWO-HOUR PERIOD IN FIVE PATIENTS

VOLUME URINE	PYRIDIUM RECOVERY	PERCENTAGE RECOVERY
3,430	655 mgm.	36.25

sample of urine. This higher concentration permits a greater precipitation with hydrochloric acid. Because of this variation in percentage of recovery, and also owing to the low percentage of recovery, the colorimetric method was then tried.

C. The colorimetric method. The colorimetric method was found to give fairly satisfactory results. This method is carried out as follows:

Ten cubic centimeters of urine containing pyridium was made up to 500 cc. with distilled water in a volumetric flask. In this dilution the light color of normal urine is negligible. This can be demonstrated by taking 10 cc. of urine

and diluting to 500 cc. with distilled water when it will be found that the mixture cannot be differentiated in the colorimeter from distilled water.

The diluted pyridium in urine, which incidently has a marked color, is compared in a colorimeter with a standard solution made by dissolving 10 mgm. of pyridium in 500 cc. of distilled water.

The usual readings are made on the colorimeter and calculations made according to the following formula:

$$C_1 = \frac{R_2}{R_1} \times C_2 \times 50$$

C_1 represents concentration of unknown pyridium in urine. R_1 represents reading on the colorimeter of the unknown, while R_2 represents the reading of the standard solution on the colorimeter. C_2 represents the concentration of standard. The constant 50 represents the relation between the diluted and undiluted urine. By multiplying C_1 by 100 we can obtain the number of milligrams in 100 cc. of urine. For example, 10 cc. of pyridium urine diluted to 500 cc. showed on colorimetric estimation that 10 millimeters of standard was matched by 28.5 millimeters of diluted unknown. By substituting in our formula, we get the following:

$$C_1 = \frac{10}{28.5} \times 0.02 \times 50 = 0.35090 \text{ mgm. per cubic centimeter of undiluted urine}$$

In 100 cc. of undiluted urine there are 35.09 mgm. of pyridium.

Table 4 gives the daily volume of urine excreted over a three-day period in this experiment. There was an average of 977 cc. per day.

Table 5 shows the daily excretion of pyridium and the percentage of recovery as determined in the colorimeter.

The complete tabulation shows a percentage of recovery by the colorimetric method ranging from 67.1 to 80.5 with an average of 74.7. It should be noted that with the colorimeter more consistent results are obtained than with the evaporation-precipitation method. The former gives higher percentages of excretion of pyridium than the latter.

Inasmuch as the pyridium in the urine is not identical with pure pyridium ingested in the experiments above, numerous experiments were conducted in order to find a ratio between the color index of pyridium eliminant and that of pure pyridium. Solutions of each in pure distilled water cannot be matched up in the colorimeter because pyridium eliminant cannot be entirely

dissolved in water. Experiments were tried in precipitating the pyridium eliminant from the urine as a mercury compound after the phosphates, oxalates, and sulphates had been removed with barium chloride and checked against pure pyridium precipitated from solution with mercury salts. Our conclusions from these experiments only served to show that pyridium and pyridium eliminant were not the same chemically since they combined with different weights of mercury.

D. Color index ratio. Ten milligrams of pure pyridium was dissolved in 500 cc. of normal urine and 10 mgm. of pyridium eliminant was dissolved in another 500 cc. of normal urine using heat to aid solution of the compounds. This was easily accom-

TABLE 4

DAILY VOLUME OF URINE EXCRETED

FIRST DAY	SECOND DAY	THIRD DAY
875 cc.	1,195 cc.	861 cc.

TABLE 5

DAILY EXCRETION OF PYRIDIUM

FIRST DAY	SECOND DAY	THIRD DAY	PERCENTAGE RECOVERED
319 mgm.	428 mgm.	466 mgm.	74.7

plished. The solutions were made up accurately in volumetric flasks, cooled and final volume brought to 500 cc. The two solutions were then matched in a colorimeter and it was found on repeated trials that 30 mm. of the standard pure pyridium solution in urine was equivalent to 33.5 mm. of pyridium eliminant solution in the same urine. The ratio of color value of pure pyridium to pyridium eliminant is 0.895. Using this ratio in our calculations on the elimination of pyridium in the urine, we obtained for the seven subjects in table 5, an average of 65.7 per cent.

This colorimetric procedure gives far more constant results for elimination of pyridium in the urine and the figures are nearer

the truth with respect to the amount eliminated. This is seen by the fact that only at times do the results found by the evaporation-precipitation method approach the above. This method based on the colorimetric determination of other urine constituents is easy to carry out and like these basic methods gives better results than purely chemical methods for the estimation of substances in the urine, because of the great danger of side reactions between the reagents used and the many other compounds found in this complex excretion.

Bacteriologic studies on pyridium

Control study. As a preliminary control study the urine of ten individuals was collected twice daily, using the same precautions as described above. One cubic centimeter of urine was plated immediately with 10 cc. of nutrient agar, pH 7.2, incubated at

TABLE 6

CONTROL ON NORMAL URINE; AVERAGE COLONIES IN TEN PATIENTS

FIRST DAY	SECOND DAY	THIRD DAY
119.7	87.2	40.9

37.5°C. for twenty-four hours and results recorded. During this trial the subjects received no pyridium, the test being conducted for three days (table 6).

In view of these findings it was not considered advisable to use too dilute a culture of test organisms in the actual trials with pyridium urine.

The bacteriological studies were conducted on twenty-seven normal individuals taking 0.6 gram pyridium a day for fourteen days. Urine was collected twice daily under aseptic conditions, as far as this was possible. Sterile containers were used to receive the urine. Only male subjects were used. The penis was thoroughly cleaned before urination and the first portion rejected. Ten cubic centimeter samples of urine were inoculated with 0.1 cc. of a 1:10 dilution of a twenty-four hour culture of the organism studied. Controls were run using 10 cc. of broth inoculating each with 0.1 cc. of a 1:10 dilution of organism. These always exhibited growth, showing viable organisms. Cultures were incubated at 37.5°C. for twenty-four hours and results recorded. The

control and the urine cultures were then plated, using 10 cc. of nutrient agar, pH 7.2, and 1 cc. of culture. The plates were incubated at 37.5° for twenty-four hours and results recorded. The original urine cultures were then incu-

TABLE 7

SUBJECT: G. S. ORGANISM: STAPHYLOCOCCUS

DAY	TIME	CONTROL CULTURE IN BROTH	URINE CULTURES			COLONIES PER PLATE		
			24 hours	48 hours	72 hours	24 hours	48 hours	72 hours
1	A.M.	+	−	−	+	0	2	u
1	P.M.	+	−	−	+	0	11	u
2	A.M.	+	−	−	−	0	0	0
2	P.M.	+	−	−	+	0	3	u
3	A.M.	+	−	−	−	0	0	0
3	P.M.	+	−	−	−	0	0	7
4	A.M.	+	−	−	−	0	0	0
4	P.M.	+	−	−	−	0	0	0
5	A.M.	+	−	−	−	0	0	0
5	P.M.	+	−	−	−	0	13	8
6	A.M.	+	−	−	−	0	0	0
6	P.M.	+	−	−	−	0	0	0
7	A.M.	+	−	−	−	0	0	0
7	P.M.	+	−	−	−	0	0	0
8	A.M.	+	−	+	+	50	u	u
8	P.M.	+	−	+	+	79	u	u
9	A.M.	+	−	+	+	0	u	u
9	P.M.	+	−	−	−	10	u	u
10	A.M.	+	−	−	+	14	103	u
10	P.M.	+	−	−	+	2	81	u
11	A.M.	+	−	+	+	7	u	u
11	P.M.	+	−	+	+	13	u	u
12	A.M.	+	−	+	+	0	73	u
12	P.M.	+	−	−	+	4	51	u
13	A.M.	+	−	+	+	0	u	u
13	P.M.	+	−	+	+	6	u	u
14	A.M.	+	+	+	+	179	u	u
14	P.M.	+	−	+	+	15	u	u

The twenty-four, forty-eight, and seventy-two-hour control plates were all uncountable.

+ = growth; − = no growth; u = uncountable.

bated at 37.5°C. for a third period of twenty-four hours, plated and results recorded. In this way the prolonged action of pyridium excreted in the urine could be studied in the case of each organism used.

The complete reports of Staphylococcus and *Esch. coli* bacteriologic studies

on the urines of individuals receiving pyridium were made after the plan of table 7, which constitutes a sample Staphylococcus protocol on one of the twenty-seven individuals. The data thus collected were recorded for each individual

TABLE 8

SUBJECT: J. J. McG. ORGANISM: ESCH. COLI

DAY	TIME	CONTROL CULTURE IN BROTH	URINE CULTURES			COLONIES PER PLATE		
			24 hours	48 hours	72 hours	24 hours	48 hours	72 hours
1	A.M.	+	−	−	−	10	4	0
1	P.M.	+	−	−	−	18	6	14
2	A.M.	+	−	−	−	0	0	3
2	P.M.	+	−	−	−	0	14	1
3	A.M.	+	−	−	−	0	0	1
3	P.M.	+	−	−	−	0	4	6
4	A.M.	+	−	−	−	0	0	16
4	P.M.	+	−	−	−	1	1	1
5	A.M.	+	−	−	+	0	11	u
5	P.M.	+	−	−	+	7	2	u
6	A.M.	+	−	−	+	3	16	u
6	P.M.	+	−	−	−	6	0	17
7	A.M.	+	−	−	−	22	17	39
7	P.M.	+	−	−	+	34	6	u
8	A.M.	+	−	−	+	10	16	u
8	P.M.	+	−	+	+	17	40	u
9	A.M.	+	−	−	−	2	0	9
9	P.M.	+	−	−	−	4	11	5
10	A.M.	+	−	−	−	5	7	1
10	P.M.	+	−	−	−	1	4	0
11	A.M.	+	−	−	−	4	2	7
11	P.M.	+	−	−	−	22	11	16
12	A.M.	+	−	−	−	0	6	2
12	P.M.	+	−	−	−	0	4	12
13	A.M.	+	−	−	+	6	23	u
13	P.M.	+	−	−	+	6	9	u
14	A.M.	+	−	−	+	17	29	u
14	P.M.	+	−	−	+	4	18	u

The twenty-four, forty-eight, and seventy-two-hour control plates were all uncountable.

in the series of twenty-seven cases and for each of the test organisms used, namely, *Esch. coli* and *Staphylococcus aureus*. (See tables 7 and 8.)

Study of patients taking 0.3 gram pyridium three times daily. A test was made of the urine of several individuals who were

taking 0.3 gram of pyridium three times a day. The technique was the same as that followed in the case of the individuals taking 0.2 gram three times a day. It is apparent from the table that

TABLE 9

SUBJECT: A. G. ORGANISM: ESCH. COLI

DAY	TIME	CONTROL CULTURE IN BROTH	URINE CULTURES			COLONIES PER PLATE		
			24 hours	48 hours	72 hours	24 hours	48 hours	72 hours
1	A.M.	+	−	−	+	74	88	u
1	P.M.	+	−	−	+	84	56	u
2	A.M.	+	−	−	+	60	99	u
2	P.M.	+	−	−	+	19	65	u
3	A.M.	+	−	−	+	71	100−	u
3	P.M.	+	−	−	+	46	34	u
4	A.M.	+	−	−	+	88	38	u
4	P.M.	+	−	−	+	42	28	u
5	A.M.	+	−	−	+	105	45	u
5	P.M.	+	−	−	+	38	63	u
6	A.M.	+	−	−	+	13	121	u
6	P.M.	+	−	−	+	20	67	u
7	A.M.	+	−	−	+	22	80	u
7	P.M.	+	−	−	+	46	47	u
8	A.M.	+	−	−	+	111	49	u
8	P.M.	+	−	−	+	74	35	u
9	A.M.	+	−	−	+	13	66	u
9	P.M.	+	−	−	+	101	39	u
10	A.M.	+	−	−	+	68	84	u
10	P.M.	+	−	−	+	44	100	u
11	A.M.	+	−	−	+	56	46	u
11	P.M.	+	−	−	+	81	20	u
12	A.M.	+	−	−	+	70	68	u
12	P.M.	+	−	−	+	103	59	u
13	A.M.	+	−	−	+	44	47	u
13	P.M.	+	−	−	+	81	86	u
14	A.M.	+	−	−	+	54	77	u
14	P.M.	+	−	−	+	89	51	u

The twenty-four, forty-eight, and seventy-two-hour control plates were all uncountable.

there is no distinct advantage due to the increased dosage of pyridium (table 9).

Tests of catheterized urine. It was considered desirable to obtain catheterized specimens of urine from individuals taking

pyridium. The usual dose of 0.6 gram per day was given, and a daily catheterized specimen of urine was used for inoculation with *Esch. coli* and Staphylococcus. The tests were carried out for a period of seven days and one sample collected daily. In all other respects the experiments were carried out as in the previous work. Table 10 shows the results obtained with one individual.

TABLE 10

SUBJECT: F. L. H. ORGANISM: STAPHYLOCOCCUS

DAY	CONTROL CULTURE IN BROTH	URINE CULTURES			COLONIES PER PLATE		
		24 hours	48 hours	72 hours	24 hours	48 hours	72 hours
1	+	−	−	+	11	47	u
2	+	−	+	+	9	u	u
3	+	−	−	−	16	0	0
4	+	−	−	−	3	0	0
5	+	−	+	+	8	u	u
6	+	−	−	−	13	2	0
7	+	−	−	+	5	14	u

SUMMARY

The experiments dealing with the excretion of Pyridium in the urine as determined by the evaporation and precipitation method showed a range of recovery from 12.7 per cent to 56.1 per cent. This wide range might be explained by a difference in pH of the urine containing the pyridium eliminant. The colorimetric determinations were more constant; these showed a range of recovery from 67.1 per cent to 80.5 per cent, with an average of 74.7 per cent. The percentage of 65.8 based on the color index ratio was accepted as final.

The bacteriologic experiments showed a definite bacteriostatic action of pyridium against *Staphylococcus aureus* and *Esch. coli* when comparison was made between the test plates and the control plates. The bacteriostatic action was more constant than the bactericidal action. The bactericidal action showed a wide variance at times; the test plates showing no growth on some days. In the above experiments the dose of Pyridium was the usual one of 0.6 gram per day. Increasing the dosage to 0.9

gram per day did not appreciably affect the bacteriostatic and bactericidal findings.

Experiments in which the usual dose of pyridium was given and the urine samples obtained by catheterization showed bacteriostatic and bactericidal action against the test organisms, Staphylococcus and *Esch. coli*.

REFERENCE

(1) GOERNER, A., AND HALEY, F. L.: A study of the antibacterial properties of Pyridium, urinary antiseptic. Jour. Lab. and Clin. Med., **16**: 957–966. 1931.

AN EXPERIMENTAL STUDY OF THE ACTION OF PHENYLHYDRAZINE HYDROCHLORIDE AND ACETYLPHENYLHYDRAZINE (PYRODIN), WITH REFERENCE TO THEIR USE IN THE TREATMENT OF POLYCYTHEMIA VERA*

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Phenylhydrazine-hydrochloride ($C_6H_5 \cdot NH \cdot NH_2 \cdot HCl$) has become the most widely used therapeutic agent in polycythemia vera, despite its known effects as a powerful protoplasmic poison. Those who have considered the drug from the standpoint of its possible deleterious action in man have come to the general conclusion that in therapeutic doses, even though administered for an indefinite period, it is not particularly injurious. Admittedly, this compound has been used with comparative success, and perhaps for this reason most clinicians have overlooked the probable advantages of acetylphenylhydrazine, a substance equally effective in blood destruction, but which, certainly in acute intoxications, produces much less damage to the organism than phenylhydrazine. That the use of phenylhydrazine-hydrochloride involves a considerable element of danger has been noted by several clinicians, notably Giffin and Conner,[9] Gouwens,[10] and McNamara and Sansum.[14]

Stimulated by the researches of Fischer[7] on the reactions of phenylhydrazine with the aldehyde and ketone groups of carbohydrates, Hoppe-Seyler[12] investigated the effects of this compound in the animal organism. He determined that the action of the compound on the blood consisted in the formation of a characteristic, but hitherto unknown brown pigment, exhibiting sharply-

* Read before the Eleventh Annual Convention of the American Society of Clinical Pathologists, New Orleans, Louisiana, May 6–9, 1932.

defined absorption bands, which, however, changed readily into a substance that could not be distinguished by its absorption spectrum. The behavior of the free base, according to Hoppe-Seyler, differed from that of the hydrochloride in that, in the absence of oxygen, it converted the hemoglobin into hemochromogen.*

Following Hoppe-Seyler, experimental studies have dealt mainly with the effects of phenylhydrazine in producing experimental anemia, with alterations in the leukocyte picture and with the questions of hepatic and renal damage.

Interest in the toxicology of acetylphenylhydrazine, or pyrodin ($C_6H_5 \cdot NH \cdot NH \cdot CO \cdot CH_3$) was first aroused as a result of its short-lived use as an antipyretic. In demonstrating the remarkable antifebrile effects of this drug, Dreschfeld[5] mentioned that slight toxic effects, consisting of jaundice and hemoglobinemia, were occasionally noticed after repeated doses of from 8 to 12 grains. Although a considerable literature has grown up on the subject, many details of the action of the compound remain obscure.

At the present time it would seem that a compound possessing the properties of phenylhydrazine is indispensable in the treatment of polycythemia, and for this reason precise knowledge of the action of this compound and of its derivatives should be of value. The experiments in the present paper were planned with the object of comparing the effects of phenylhydrazine-hydrochloride and acetylphenylhydrazine when administered in moderate doses over a period of several months. The dosage was such that for considerable intervals the erythrocyte counts were maintained at approximately half the normal values.

* Hoppe-Seyler conceived the so-called hemochromogen spectrum to be due to a relatively simple substance, $C_{34}O_{35}N_4O_4Fe$. The present view, which is based largely on the work of Anson and Mirsky in Barcroft's laboratory, is that the characteristic spectrum attributed to hemochromogen is given by a conjugated protein consisting of hemoglobin and the base heme, $C_{34}H_{32}N_4O_4Fe$. Synthetic hemochromogens, compounds of heme with a large variety of nitrogenous substances, including hydrazine and phenylhydrazine, give absorption spectra which sufficiently resemble that of the heme-globin compound as to be mistaken for it. For a detailed discussion see ANSON, M. L., AND MIRSKY, A. E.: Physiol. Rev., **10**, 506–546. 1930.

PROTOCOL 1

RABBIT M-1: PHENYLHYDRAZINE-HYDROCHLORIDE

DATE (1931)		ERYTHROCYTES	HEMOGLOBIN	LEUKOCYTES	BASOPHILES	EOSINOPHILES	MYELOCYTES	JUVENILES	"STAB"	SEGMENTED	LYMPHOCYTES	MONOCYTES	DOSE	REMARKS
		millions	*grams per 100 cc.*	*thousands*									*mgm.*	
January	5	4,70	11.36	6,9					2	52	40	6		Weight 3.1 kgm.
	8	4,89	11.36	6.1										
	12	4,59	11.78	5,5						41	53	6		
	13												40	
	15	4,21	7.19	10,5		4		1	2	40	49	4		Microcytes, toxic lymphocytes and marked polychromasia
	17	3,21	6.53	11,3										
	20	2,43	7.45	7,25			1		3	31	57	8		Marked polychromasia, anisocytosis and poikilocytosis
	22	3,00	8.34	4,35										
	24	3,86	9.62	4,75						42	54	2	20	Weight 3.1 kgm.
	29	4,63	10.22	2,75		6				14	76	4		Many toxic lymphocytes
	30												50	
February	3	3,05	6.32	12,3	3	1				40	55	1		
	10	4,09	9.74	3,7										
	11												50	
	18	3,98	10.03	3,05	2	4				28	56	10		Toxic lymphocytes, microcytes, Heinz-Ehrlich bodies
	19												100	
	24	2,43	4.86	19,1	2					36	54	4		Many toxic lymphocytes, Türck cells, Heinz-Ehrlich bodies
March	3	3,70	11.15	5,1	4	2				24	68	2		
	5												50	
	19													Rabbit delivered litter of six. One died March 31
	31	4,00	10.22	7,9										3.2 kgm.
April	4												50	
	6												50	
	10												50	
	14	2,18	5.26	9,3	3		1	1	1	71	22	2		Heinz-Ehrlich bodies
	29	4,16	9.02	8,6						44	40	16		
May	5												100	
	8	2,27	5.5	11,1						70	30	0		Microcytes, Heinz-Ehrlich bodies
	20	5,05	9.77	5,8	2					34	64	0		Autopsy, ether anesthesia

PROTOCOL 2

RABBIT M-2: ACETYLPHENYLHYDRAZINE

DATE (1931)		ERYTHROCYTES	HEMOGLOBIN	LEUKOCYTES	BASOPHILES	EOSINOPHILES	MYELOCYTES	JUVENILES	"STAB"	SEGMENTED	LYMPHOCYTES	MONOCYTES	DOSE	REMARKS
		millions	*grams per 100 cc.*	*thousands*									*mgm.*	
January	5	4,70	11.00	6,9						30	65	5		Weight 2.5 kgm.
	8	5,02	11.00	9,1										
	12	4,97	11.00	6,75						32	64	4		
	13												40	
	15	4,38	7.3	9,35						26	71	3		Marked polychromasia, toxic lymphocytes
	17	2,78	5.8	11,5										
	20	2,53	7.9	7,95	6		2			13	75	4		Polychromasia, toxic lymphocytes, microcytes
	22	3,94	8.5	5,6										
	24	3,95	9.2	5,15	2					15	80	3	20	
	29	4,71	10.22	5,75	4					10	82	4		
	30												50	
February	3	3,67	6.9	10,8	3			1	2	21	72	1		Heinz-Ehrlich bodies, microcytes, polychromasia
	10	4,37	8.8	6,8										
	11												50	
	18	3,52	9.7	7,5	2	4				28	56	10		Microcytes, toxic lymphocytes
	19												100	
	24	2,93	8.0	6,5	2				4	36	54	4		Many toxic lymphocytes, Türck cells Heinz-Ehrlich bodies
March	3	4,46	11.36	3,6	4	2				20	71	3		Weight 2.9 kgm.
	5												50	
	31	5,60	14.38	6,8										Weight 3.1 kgm.
April	4												50	
	6												50	
	10												50	
	12													Weight 2.7 kgm. Rabbit delivered a litter during the night and devoured it
	14	2,84	7.0	9,2	2			2	4	52	38	1		Heinz-Ehrlich bodies
	29	6,47	10.4	21,5	4			2	6	9	75	4		
May	5												100	
	8	3,33	6.5	25,3	2	1		3	4	36	52	2		
	20	4,53	10.1	7,8	1	1			4	34	56	4		Autopsy, ether anesthesia

Twelve rabbits were used in the present series. In Protocols 1 and 2 are summarized the data obtained in two of the experiments, selected for comparison.

Rabbits M-1 and M-2 were under observation for 136 days. One received 0.56 gram of phenylhydrazine hydrochloride, subcutaneously, the other a similar amount of acetylphenylhydrazine. Both were autopsied two weeks after the last dose. Rabbits M-3 and M-4 were under observation for 171 days, during which M-3 received 0.68 gram of acetylphenylhydrazine and M-4 a similar amount of phenylhydrazine hydrochloride. The animals were sacrificed five days after the last dose. Rabbits M-8, M-9, and M-10 were under observations for 277 days. M-8 received a total of 0.5 gram of phenylhydrazine hydrochloride, in small periodic doses, and M-9 and M-10 similar amounts of acetylphenylhydrazine. In each case the last dose was given on the 154th day and autopsies were performed 123 days later.

GENERAL EFFECTS ON THE BLOOD

The destruction of erythrocytes is a prominent feature, but is frequently delayed, except following the administration of very large doses. There is considerable variability in the effect of a given dose of either phenylhydrazine or its acetyl derivative and it is therefore difficult to evaluate their relative actions, but as far as can be judged from the present experiments and earlier observations, the two compounds are approximately equally effective. The increased tolerance to these drugs which various authors have described both in experimental and clinical studies is probably not a property acquired by the organism, but is inherent in the cells. Newly-formed erythrocytes seem to be more resistant to their action than older, more mature corpuscles. If sufficiently long intervals are allowed between injections (four to six weeks), repeated doses seem to have about the same effect.

Of particular interest are the changes in the composition of the erythrocytes. In anemia produced by both phenylhydrazine and acetylphenylhydrazine the volume of the average corpuscle increases, often more than 50 per cent (Bodansky[2]). There is a

definite and disproportionate increase in the water content of the corpuscle (Bodansky and Dressler[3]) and a corresponding fall in its specific gravity (unpublished data), a relative decrease of the hemoglobin (often there is a rise in the absolute amount per cell), and an increase of the non-hemoglobin protein fraction. The average erythrocyte in the experimental anemia produced by these drugs also differs from the normal in containing cholesterol esters and an increased amount of unsaturated fatty acids.

In addition to these changes in chemical composition are the alterations in the physical appearance of the cells. Attention has been called recently by Bratley and associates[4] to the formation of dense, refractile bodies within the cells. These bodies, named after Heinz[11] and Ehrlich[6] have been previously observed, but their significance is not clearly understood. According to Bratley, these "inner bodies" apparently result from a primary condensation of the hemoglobin and the drug, followed by the formation of semifluid bodies which fuse and become semisolid. Heinz-Ehrlich bodies were observed from time to time in all of our experimental animals. Whatever the mechanism for their formation may be, they obviously represent an alteration in the physicochemical properties and distribution of the hemoglobin. The recent observations of Warburg, Kubowitz and Christian[16] bear closely upon this problem. They found that rabbit cells treated with phenylhydrazine and suspended in a suitable, glucose-containing medium, exhibited a ten to twelvefold increase in respiration and in the capacity to oxidize the glucose. The phenomenon is attributed to the catalytic effect of the hemin which is liberated in the reaction between phenylhydrazine and hemoglobin, the other product of the reaction being globin, as shown by the fact that when the phenylhydrazine-treated cells are hemolyzed, denatured globin separates out. The outward diffusion of the hemin and the retention of the globin probably explains the increase in the non-hemoglobin fraction to which reference has been made. Warburg suggests that the reaction with phenylhydrazine may also affect the young cell at the site of its formation, a point which merits close study. With regard to the increased non-hemoglobin protein content of

the erythrocytes formed during rapid regeneration, it is obviously to be associated with the high proportion of nucleated cells and reticulocytes. The latter may reach very high levels, reticulocyte counts as high as 76 per cent having been encountered in our experiments. That the changes in the constitution of the erythrocytes profoundly alter their physical and chemical properties is to be assumed, but in the further pursuit of the problem, it will be necessary to distinguish the chemical peculiarities of the injured corpuscles from those of the newly-formed and immature erythrocytes.

Long[13] found no relation between leukocytosis and the injection of phenylhydrazine in his experiments with rabbits. On the other hand, Giffin and Allen[1,8] observed a definite, though somewhat irregular tendency toward an increase in the number of leukocytes, and many clinicians have had the same experience in the therapeutic use of phenylhydrazine. In the present series of experiments the majority of rabbits exhibited leukocytosis with considerable regularity. Not infrequently the leukocytosis was followed by a sharp fall to very low levels, at the expense of the granulocytes (for example rabbit M-1, June 29, Feb. 10 and 18). No definite change in the proportion of mononuclears could be determined. The drugs did not produce any very marked shift to the left, as determined by the Schilling count. Myelocytes and even juvenile forms were encountered very infrequently and the stab forms showed only a slight tendency to increase. This observation is of significance, indicating that the appearance of myelocytes and juvenile forms in cases of polycythemia treated with these drugs is probably a manifestation of the disease rather than the effect of the treatment.

ACTION ON THE HEART AND LUNGS

Except for slight acute granular degeneration in rabbits M-3 and M-5, nothing in the microscopic appearance of tissue from the heart could be attributed to the action of the drugs. Rabbits M-1 and M-8 exhibited a small amount of endocardial sclerosis, but were otherwise normal. Rabbit M-10 showed marked fatty invasion of the heart, probably nutritional in origin.

The rabbits which were examined after death by deep ether anesthesia showed edema and marked congestion in the lungs. In the others, the lungs were normal in appearance.

ACTION ON THE KIDNEY

Autopsies were performed on rabbits M-3 (pyrodin) and M-4 (phenylhydrazine-HCl) five days after the final dose. The former showed marked acute degeneration and engorgement; the latter showed extensive degenerative and necrotic changes affecting especially the convoluted tubules. The glomeruli were markedly engorged.

Rabbit M-1 (phenylhydrazine-HCl) and M-2 (pyrodin) were examined at autopsy two weeks after the final injection. Rabbit M-1 showed hydropic changes in the collecting tubules, acute tubular degeneration and extravasation of blood into the glomeruli. Rabbit M-2 showed moderate engorgement and acute degeneration.

Rabbits M-8, 9 and 10 were examined at autopsy 123 days after the drug was discontinued. Rabbit M-8 showed a slight amount of nephrosclerosis; in M-10 there was evidence of a previous degenerative change, and in M-9 nothing unusual was observed.

It appears therefore that both phenylhydrazine and acetylphenylhydrazine are nephrotoxic, the former somewhat more than the latter, and that, if the drugs are discontinued after moderate doses, the damage is largely repaired.

ACTION ON THE LIVER AND SPLEEN

Rabbits M-1 and M-2 showed acute degeneration, of moderate severity, and congestion. M-4 showed marked fatty degeneration and central necrosis; in M-3 the degenerative changes were more limited. The livers of rabbits M-8, M-9 and M-10 were normal and showed no evidence of cirrhosis.

Although in acute intoxications, the spleen may enlarge considerably, in the more chronic conditions, grossly it often appears atrophic. On microscopic examination, the spleens of rabbits M-1, M-2, M-3 and M-4 were found to be congested and to contain abnormal amounts of pigment. Rabbit M-3 showed in

addition a subacute perisplenitis. Rabbit M-8 had a low grade splenitis and in rabbits M-9 and M-10, there was marked fibrosis.

CHANGES IN THE BONE MARROW

The bone marrow of the experimental animals was carefully compared with that of normal animals of about the same age. In M-1, M-2, and M-4 there was evidence of an erythroblastic hyperplasia. In rabbit M-3, the bone marrow was fatty; in M-8, M-9 and M-10 it appeared essentially normal.

ADRENALS AND BRAIN

Bratley and associates have described the occurrence of focal myeloid metaplasia in the adrenal cortex of rabbits poisoned with pyrodin. In our experiments, the adrenals remained normal. This may have been due to the difference in dosage.

Careful examination of the brains of our animals revealed nothing remarkable. In this connection, reference may be made to the interesting observation of Mosse and Rothmann[15] that in dogs made severely anemic with pyrodin, there occurred marked degeneration of the posterior columns of the cord.

SUMMARY AND CONCLUSIONS

1. Acetylphenylhydrazine and phenylhydrazine-hydrochloride produce approximately the same grade of anemia in the rabbit.

2. The apparent tolerance to these drugs which is established is probably not a property acquired by the organism, but is inherent in the corpuscles formed during rapid regeneration. These are more resistant than normal cells probably because of differences in chemical composition.

3. A striking feature of the differential leukocyte count (Schilling) during treatment with these compounds is that there is only a slight tendency toward a shift to the left.

4. Both compounds are toxic, the liver and kidney being especially susceptible to injury. The changes which occur in these organs in chronic intoxications of moderate severity are apparently not permanent, for in animals autopsied several months after discontinuing the drugs, no active lesions were

found, although in two of the animals there was evidence of a previous degenerative change in the kidneys.

5. While a quantitative comparison of the effects of phenylhydrazine-hydrochloride and acetylphenylhydrazine in causing tissue damage cannot be made, the impression is nevertheless definite that the latter compound is less toxic than the former.

6. Assuming that a compound of the type of phenylhydrazine is essential in the treatment of polycythemia vera, it would therefore appear that acetylphenylhydrazine is to be preferred to phenylhydrazine-hydrochloride.

REFERENCES

(1) Allen, E. V., and Giffin, H. Z.: Experiments with phenylhydrazine. Ann. Int. Med., **1,** 677–682. 1927–1928.

(2) Bodansky, M.: The distribution of unsaturated fatty acids, cholesterol, and cholesterol esters in experimental anemia. Jour. Biol. Chem., **63,** 239–251. 1925.

(3) Bodansky, M., and Dressler, O. G.: The distribution of water and cholesterol in the blood in experimental anemia. Quart. Jour. Exp. Physiol., **17,** 157–160. 1927.

(4) Bratley, F. G., Burroughs, H. H., Hamilton, D. M., and Kern, C.: The effect of pyrodin poisoning on the blood and hemolytopoietic system. Am. Jour. Med. Sci., **182,** 597–605. 1931.

(5) Dreschfeld, J.: Pyrodin; A new antipyretic. Brit. Med. Jour., **2,** 881. 1888.

(6) Ehrlich, P.: Ueber schwere anämische Zustande. Kong. f. inn. Med., **11,** 33–64. 1892.

(7) Fischer, E.: Phenylhydrazin als reagens auf aldehyde und ketone Ber. d. deutsch. chem. Gesellsch., **17,** 572–578. 1884.

(8) Giffin, H. Z., and Allen, E. V.: Experiments with phenylhydrazine. Ann. Int. Med., **1,** 655–676. 1927–28.

(9) Giffin, H. Z., and Conner, H. M.: The untoward effects of treatment by phenylhydrazine-hydrochloride. Jour. Am. Med. Assn., **92,** 1505–1507. 1929.

(10) Gouwens, W. E.: Polycythemia vera. Woodlawn Hosp. Clin. Quart., **1,** 27–31. 1931.

(11) Heinz, R.: Morphologische Veränderungen der rothen Blutkörperchen durch Gifte. Arch. f. path. Anat., **122,** 112–116. 1890.

(12) Hoppe-Seyler, G.: Ueber die Wirkung des Phenylhydrazins auf den Organismus. Ztschr. f. physiol. Chem., **9,** 34–39. 1885.

(13) Long, P. H.: Experimental anemia produced by phenylhydrazine derivatives. Jour. Clin. Inv., **2,** 329–342. 1926.

(14) McNamara, D. H., and Sansum, W. D.: Phenylhydrazine poisoning: Report of a case. Jour. Am. Med. Assn., **96,** 268–269. 1931.

(15) Mosse, M., and Rothmann, M.: Ueber Pyrodinvergiftung bei Hunden. Deutsch. med. Wchnschr., **32,** 134–138. 1906.

(16) Warburg, O., Kubowitz, F., and Christian, W.: Über die Wirkung von Phenylhydrazin und von Phenylhydroxylamin auf die Atmung roter Blutzellen. Biochem. Ztschr., **233,** 240–242. 1931.

A CHART AND SYSTEM FOR REPORTING AND RECORDING BLOOD EXAMINATIONS

FRED. BOERNER

From the Laboratories of the Graduate Hospital of the University of Pennsylvania; Contributed under the Diagnostic Hospital Endowment

The methods now in common use for reporting and recording blood examinations offer many possibilities of error and misinterpretation which, with our present knowledge of the subject, could be remedied to a remarkable degree. Indeed the more improvement in the method of reporting and recording hematological examinations, the greater will be their value to the clinician with a better and more accurate correlation with other clinical signs.

The commonest causes of error and misinterpretation are well known and the remedy for most of these is simple while other remedies, although simple, appear complicated or radical.

The system for reporting blood examinations discussed in this publication, is simple and yet offers to the clinician a means of interpreting the results with a far greater degree of accuracy and the minimum of mental burden.

In the past too little attention has been given to normal ranges and too much attention to average normals. The average clinician wishes to know when a patient is below or above normal. This can only be answered by a knowledge of the normal range and to him the average normal is of little or no value. He works with high and low normals for blood sugar and has not worried about an exact average normal. The use of the percentage system for reporting results is mathematically unsound and no doubt accounts for many errors in interpretation. For example, a given percentage of hemoglobin can have as high as ten different values when expressed in grams per 100 cc. of blood. The percentages given in all texts for the various types of leukocytes are applicable to normal counts only.

FORM 186 770

GRADUATE HOSPITAL
UNIVERSITY OF PENNSYLVANIA

Name R T
Room or Ward 217
Case No.

BLOOD CHART

Hb GRAMS	ERYTHROCYTE NUMBER		A.M. P.M.																		
		MO.	11	11	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
		DAY	30	30	1	2	2	3	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
18	7.00																						
17	6.50																						
16	6.00																						
15	5.50																						
14	5.00																						
13	4.50																						
12	4.00																						
11	3.75																						
10	3.50																						
9	3.25																						
8	3.00																						
7	2.75																						
6	2.50																						
5	2.25																						
4.5	2.00																						
4.	1.75																						
3.5	1.50																						
3.	1.25																						
2.5	1.00																						
2.	.75																						

TRANSFUSION				250 c.c.			250 c.c.		250 c.c.		250 c.c.		250 c.c.		250 c.c.		250 c.c.		250 c.c.		250 c.c.		350 c.c.	
Achromia			—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Anisocytosis			+1	—	+1	+1		+1		+1	+1	+1	+1	+1	+1	+1	+1	+1	+1	+1	+1	+1	+1	+1
Poikilocytosis			—	—	—	—		—		—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Polychromatophilia			—	—	—	—		—		—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Basophilic Deg.			—	—	—	—		—		—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Nucleated Erythrocytes			—	—	1	2		2		2	—	—	5	—	—	—	6	1	—	—	—	1		
Reticulocytes				0.4																				
Color Index			0.7	0.7	0.7	0.7		0.7		0.7	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.7	0.8	0.7	0.7
Volume Index																								
Saturation Index																								

LEUKOCYTES	NUCLEAR INDEX
Over 200,000	Over 15
1-200,000	15
80-100,000	14
25- 80,000	13
20- 25,000	12
16- 20,000	11
12- 16,000	10
10- 12,000	9
8- 10,000	8
7- 8,000	7
6- 7,000	6
5- 6,000	5
4- 5,000	4
3- 4,000	3
2- 3,000	2
1- 2,000	1
500- 1,000	0.5
250- 500	0.1
Under 250	—

	M	N	N	N	N

O=Erythrocyte Count
X=Hemoglobin (red ink)
—=None
+1=Slight
+2=Moderate
+3=Marked
+4=Very Marked
N=Neutrophiles
L=Lymphocytes
M=Monocytes
E=Eosinophiles
B=Basophiles
X=Nuclear Index (red ink)
P=Platelets

See Reverse Side for Normals Remarks

STANDARD NORMALS AND NORMAL RANGE*

EXAMINATION	STANDARD NORMAL (100 per cent)	NORMAL RANGE
Hemoglobin (male)	17.3 gms. per 100 cc. of blood	14–18 gms. (80–105 per cent) per 100 cc. of blood
Hemoglobin (female)	17.3 gms. per 100 cc. of blood	12–15.5 gms. (70–90 per cent) per 100 cc. of blood
Erythrocytes (male)	5 million	4.5 to 6 million
Erythrocytes (female)	5 million	4 to 5.5 million
Leukocytes	According to age (see below)	4 to 11 thousand
Cell volume (male)	50 cc. per 100 cc. of blood	40 to 50 c.c. per 100 m. of blood
Cell volume (female)	50 cc. per 100 cc. of blood	35 to 45 cc. per 100 cc. of blood
Volume per cent (male)	Double the cell volume	80 to 100 per cent
Volume per cent (female)	Double the cell volume	70 to 90 per cent

NORMAL RANGE OF LEUKOCYTES*

	3 MONTHS TO 3 YEARS	3 TO 5 YEARS	OVER 5 YEARS AND ADULTS
Neutrophiles	2000–7000	3000–8000	3000–7000
Basophiles	0–50	0–50	0–50
Eosinophiles	25–700	50–700	50–400
Lymphocytes	4000–9000	2500–6000	1000–3000
Monocytes	25–700	25–700	100–600

NUCLEAR INDEX*

15 or over—*Normal*
10 to 15—Very slight shift to the left
5 to 10—Slight shift to the left
Under 5—Marked shift id the left

* These figures are taken from Approved Laboratory Technic by Kolmer and Boerner, D. Appleton & Co., New York, N. Y., 1931.

REMARKS

11-30-31 No clott retraction
Bleeding time 10 minutes
Coagulation time 5 minutes

12-1-31 Icterus index 6
Van den Bergh direct negative
indirect 0.3

12-9-31 Fragility test 0.44% to 0.30%

For several years I have been devoting attention to this phase of hematology with the result that more acceptable methods have been formulated for reporting leukocyte counts,[1] "shifts to the left"[3] and for calculating indices. These methods have been given several years trial and found very satisfactory and helpful and by their use, the results are much more satisfactory for charting or graphing.

To complete the system a chart* has been drafted which will permit of charting or graphing all the various blood examinations now in common use. The chart was designed with the hope of offering to the clinician a method for charting blood reports which would give some of the advantages that the temperature chart has given. The chart is especially useful in cases of blood dyscrasias and in cases requiring several examinations from time to time. All the blood reports are on one sheet and changes can be noted at a glance. Additional assistance is given by having the normal ranges on the back of each chart together with a space for remarks. The figures given for the ranges are taken from Approved Laboratory Technic by Kolmer and Boerner and which have been discussed in more detail elsewhere.[2]

It is to be clearly understood that the use of the system here described does not in any way improve the accuracy of the various examinations or in any way compensate for the errors in technic or inferior methods used for conducting the tests. However, the system is submitted as a more accurate aid for the detection of changes than the usual methods now in use.

HEMOGLOBIN

The results of the hemoglobin estimations are reported in grams per 100 cc. of blood and indicated on the chart by (x), preferably in red ink. The mark is placed opposite the figure on the scale to which the reading most closely corresponds. If the reading is half way between two of the figures it can be placed on the line dividing them. The two heavy lines represent the low normal ranges, the lower for females and the upper for males. The

* These charts can be purchased from the Keystone Printing Co., 12 S. 10th St., Philadelphia, Pa.

purpose of these lines is to enable the clinician to see at a glance how near or far from normal are the results reported and recorded. It is not expected that these ranges are to be accepted as absolute low normals. They are however, close enough to the usual accepted figures to be of practical value.

The clinician who is still unaccustomed to the gram method and desires to know about what percentage a certain number of grams represents can readily convert the number of grams into percentage by multiplying the number of grams per 100 cc. of blood by 6:

$$6 \times \text{grams per 100 cc.} = \text{per cent of hemoglobin}$$

The exact factor to multiply by to convert grams into percentage so as to correspond to the standard normal is 5.78. The figure given above is close enough however, for practical use and is more convenient.

ERYTHROCYTES

The erythrocyte count is expressed in millions and fractions thereof and is indicated by the mark (o) which is placed opposite the figure on the scale to which it most closely corresponds. The heavy lines represent the low normal ranges, the lower for females and the upper for males (see discussion under hemoglobin).

Various abnormal changes of the erythrocytes commonly reported upon are listed and the degree of change indicated by +1, +2, etc. The reticulated cells are recorded in per cent and the nucleated cells in number appearing in the differential count.

COLOR INDEX

The color index is calculated by multiplying the number of grams of hemoglobin by 3 and dividing by the first two numbers of the erythrocyte count.

$$\frac{3 \times \text{grams of hemoglobin}}{\text{First two numbers of the erythrocyte count}} = \text{Color index}$$

The exact factor to multiply the hemoglobin by is 2.89 to make it correspond to standard normal. However, the figure recommended will give indices very close to those obtained with standard normal and is more practical and convenient.

VOLUME INDEX

The volume index is calculated by dividing the number of packed cells per 100 cc. of blood by first two numbers of the erythrocyte count.

$$\frac{\text{Cubic centimeters of packed cells per 100 cc. of blood}}{\text{First two numbers of the erythrocyte count}} = \text{Volume index}$$

SATURATION INDEX

The saturation index is calculated by multiplying the number of grams of hemoglobin by 3 and dividing by the number of packed cells per 100 cc. of blood.

$$\frac{3 \times \text{grams of hemoglobin}}{\text{Cubic centimeters of packed cells per 100 cc. of blood}} = \text{Saturation index}$$

The exact factor for multiplying the hemoglobin by is 2.89 as stated under color index.

LEUKOCYTES

The total count is not reported or recorded in this system. There does not appear to be any logical reason for including the total count when the number of each type of cell is given and the total leukocyte count so readily computed by adding these together. However, since the use of total counts has become so well established it may be desired by some to have it reported and charted, in which case it can be indicated on the chart by the letter "T." The chart will not show the exact count but will indicate that is between certain figures which is sufficiently accurate for practical clinical purposes.

The number of each type of cell per cubic millimeter is reported and recorded. The various types are indicated by letters, e.g.: "N" for neutrophiles, "L" for lymphocytes, etc. The letter is placed opposite the number on the scale to which the report most closely corresponds, e.g., if the number of neutrophiles is found to be 4,350, the letter N is placed on the line opposite 4-5000. Percentages are omitted entirely as this system of reporting leukocytes is given in all texts, applicable to normal counts only and

therefore difficult to interprete in abnormal counts and is very often misleading.

To obtain the totals for each type separately, it is necessary first to make a total count, then determine the percentage of each type by the differential count. The calculation is made by simply multiplying the number of hundreds in the total count by the percentage of each type separately. The sum total of all types is equal to the total count.

Any report giving the total number of leukocytes and the percentages of the various types can be readily converted into actual numbers of each type by multiplying the number of hundreds in the total count by the percentages.

The normal range for each type, according to age, is given on the back of each chart. The three dark lines on the chart represent the normal ranges for the neutrophiles and lymphocytes. The neutrophiles normally fall between the top and middle lines and the lymphocytes between the middle and bottom lines, so at a glance, any abnormal changes in these cells can be recognized. All of the other types fall below the bottom line according to their range. The basophiles need not be charted or even reported, as the changes in the number of these cells have practically no clinical significance except in myelogenous leukemia.

Abnormal or immature types of leukocytes can be charted by using a suitable symbol.

For reporting and recording "shifts to the left" (Nuclear index) of the neutrophiles, the nuclear index described by the writer elsewhere[2] is advocated. This method is very suitable for determining the degree of shift and simplifies it for the clinician. The index is obtained by dividing the number of mature by the number of immature neutrophiles or metamyelocytes. The normal as well as the significance of changes in the index is given on the back of each chart.

PLATELETS

In cases of purpura the platelets can be charted in the space used for leukocytes, using the leukocyte scale which ranges from more than 200,000 down. The letter P is used for indicating platelets.

TRANSFUSIONS

When a transfusion is given it can be indicated on the chart by x in the space provided and under the proper date. The amount given can be recorded under remarks on the back.

CONCLUSIONS

A system of reporting blood examinations is offered which has the following advantages: (1) A means for reporting and recording hemoglobin in grams with the least inconvenience to the clinician who is only accustomed to percentages. (2) Elimination of average normals and substitution of ranges for interpreting reports. (3) Elimination of the percentage systems for reporting hemoglobin and leukocytes. (4) Elimination of the percentage systems by new and more logical methods for calculating the various indices without disturbing the generally accepted normals. (5) A method for determining "shifts to the left" which is simple yet accurate and very amendable to charting. (6) A chart for recording or graphing the various blood examinations now in common use.

REFERENCES

(1) BOERNER, F.: Method for reporting and interpreting the leukocyte count. Jour. Lab. and Clin. Med., **16:** 296–300. 1930.

(2) BOERNER, F.: Standard normals and normal ranges in hematology. Am. Jour. Clin. Path., **1:** 391–398. 1931.

(3) GERARD, J. H., AND BOERNER, F.: The significance of "shift to the left" in differential leucocyte counts and the nuclear index as a means for interpreting and recording. I. The nuclear index of normal blood and the influence of age. Jour. Lab. and Clin. Med., **16:** 300–305. 1930.

THE PHOTO-ELECTRIC SCOPOMETER*

WILLIAM G. EXTON

From the Laboratory and Longevity Service of the Prudential Insurance Company of America, Newark, New Jersey

The measurement of transmitted light is a most important and fundamental function of the clinical laboratory because so many determinations depend upon bench manipulations which yield no information at all until the light transmission of the resulting colored solution or turbid suspension has been measured optically. For this purpose a number of different instruments are available which, by one or another modification, make it possible to ascertain the value of an unknown sample by matching its density or brightness with that of a known or standard sample of the same material.

Unfortunately, the instruments which measure color best do not measure masses in suspension so efficiently, and vice versa. It is therefore necessary for laboratories to keep on hand nephelometers and turbidimeters as well as colorimeters.

Furthermore, many biological materials such as hemoglobin, protein, indican, et cetera are either so troublesome to isolate, so scarce, or keep so poorly that their routine preparation as standards for use in colorimeters and nephelometers is hopelessly impracticable. To meet these deficiencies it is necessary to resort to a multiplicity of cruder devices which feature more or less approximate substitute standards for special determinations. Notwithstanding their lack of precision, laboratories must also have some of these on hand. Thus the cost of acquisition and upkeep as well as the necessary training for operating the variety of instruments now in use are disadvantages which laboratory directors are incessantly hoping and trying to overcome.

* Read before the Tenth Annual Convention of the American Society of Clinical Pathologists, Philadelphia, Pennsylvania, June 7–9, 1931.

Light transmission measurements are still made visually, although it is well understood that all visual measurements suffer from ineradicable aberrations and limitations which are inherent in optical physiology. As an instance, the very limited range over which Bier's law holds is not always appreciated. It is also well known that some colors are more difficult to match than others; in fact, many people never succeed in matching certain colors with confidence. It is common experience that lower and higher concentrations are measurable only in a haphazard approximate way, if indeed at all, because of too much glare in the lower and too little light in the higher densities.

Furthermore, there are not only individual differences in vision but the same person cannot always count on consistent vision, because even slight or temporary changes in mental or physical condition may affect it. In short, the human eye is not only defective but the brain back of it is also subject to physical and psychical variations. Thus, even under ideal conditions with perfect instruments and the utmost skill, visual measurements are subject to uncontrollable errors which arise from a number of different causes.

Since the discovery of conditions which translate light proportionally into electricity, many efforts have been made to eliminate the errors inseparable from visual measurements by substituting for human eyes the photo-electric effect or electric eye, as it is so often called. The theory is so perfect that it is not at all surprising to find the literature rich in descriptions of photo-electric measuring devices. On the contrary, it is rather more surprising to find that photo-electric instruments for clinical laboratory work are not yet available. The failure is, of course, attributable to practical difficulties resulting from the inconstancy of light sources, the limitations of photo-electric tubes, especially fatigability and low energy output and, in my opinion, also to the photo-electric practise of measuring light in terms of electric units.

In a previous paper I tried to show how efforts which have hitherto been made to overcome these basic difficulties ended in complicating matters with amplifying tubes and circuits, current control devices, potentiometers and other meters, and batteries

with other accessories needing temporary as well as permanent connections. As such arrangements cannot be molded into finished, self-contained instruments, they are necessarily awkward and even when operated with the utmost skill and vigilance subject to sudden deviations from standardization without warning. They are, therefore, unsuitable for the conditions which obtain in most clinical laboratories where accuracy and consistency depend so much upon the simplicity of operation and stability of measuring instruments.

In the same paper I also described experiments intended to adapt the photo-electric effect to scopometry[1,2,3,4] by trying to avoid rather than complicate the basic practical difficulties. Thus the inconstancy of light sources was balanced out by using the simplest possible classical Wheatstone bridge circuit which has nothing in it to adjust. In conjunction with this, another experiment designed to measure light transmission photo-electrically in terms of light rather than in the terms registered by electric meters, which have hitherto been used for photo-electric measurements, was also described. It was found that a combination of these principles greatly reduced the limitations of photo-electric tubes by permitting the employment, as a means of measurement, of the differential between two similar tubes. In this way amplifying troubles were found avoidable and the double advantages of a null method (electrically and optically) and maximum photo-electric tube performance gained.

The success of these experiments led me to construct two instruments which have been in continuous operation four to six hours every working day over periods of three and two years, respectively, by twenty or more individuals engaged in doing the routine and research work of the Prudential Laboratory. These instruments have proven so stable, reliable and efficient that I have ventured to entrust the Bausch & Lomb Optical Company of Rochester, N. Y. with making the Photo-Electric Scopometer available to others.

DESCRIPTION

Figure 1 shows the general appearance of the instrument, which is a self-contained unit without batteries or accessories ready for operation when con-

nected with the usual house current. It will be seen that two symmetrical optical paths run from opposite sides of the lamp house to two similar photo-electric tubes. In the left path there is a recess for the specimen cell, and in the right there are interposed two adjustable diaphragms: an iris or setting, and a rectangular or measuring diaphragm with attached speedometer scale. The apertures of both diaphragms are controlled by fine adjustments similar to those on microscopes. Directly in front of the observer and clearly visible at the same time are the galvanometer dial with its zero point slit and the scale from

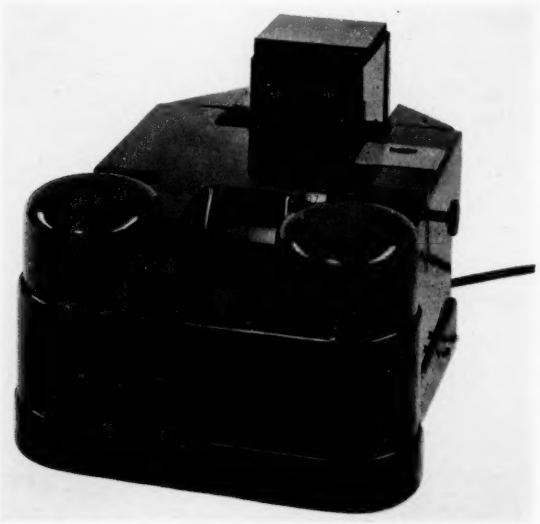

FIG. 1. ELECTRO SCOPOMETER

The optical paths lead from the lamp house to the photo cells in the front of the instrument. Note the recess on the left for the specimen; on the right the button for turning the measuring diaphragm with the setting iris-diaphragm behind it, and the switches for bridge and lamp conveniently placed together in the base.

which measurements are read. The optical system in its dust and smoke-proof housing is designed to distribute parallel light equally to both photo-electric tubes.

The electric system (fig. 2) comprises a lamp and a bridge circuit with independent switches placed conveniently together on the right side of the instrument. The lamp circuit is the usual type and the bridge circuit is the simplest conceivable, consisting of only wire and three fixed resistances. The circuits are wired hard and fast as in a radio and there is nothing in them to adjust or get

out of order. The other electric parts are the photo-electric tubes, the galvanometer and the lamp.

The photo-electric tube is, of course, the heart of any photo-electric measuring device. There are many different kinds on the market, but I have experienced the greatest difficulty in securing tubes which I considered efficient for photometry. In fact, I feel greatly obligated to Dr. H. C. Rentschler, Research Director of the Westinghouse Company, for his interest and skill in providing special tubes for the scopometer which answer every clinical pathological necessity and which he is able to reproduce so very closely. The color sensitivity of Dr. Rentschler's tubes leans a little more to the blue end of the spectrum than does the human eye, but they are more than red sensitive enough to measure efficiently

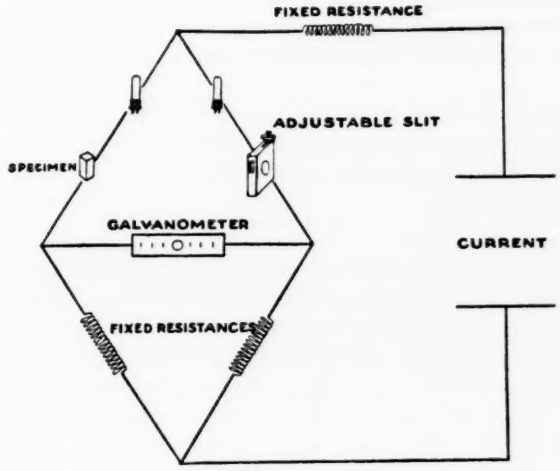

FIG. 2. PHOTO-ELECTRIC SCOPOMETER CIRCUIT

Note that all electrical connections are permanent and there are no electrical adjustments of any kind.

hemoglobin and the other yellow, red and brown compounds of clinical pathological interest, without filters of any kind. They are free from fatigue and dark current effects and, above all, they are so sensitive to turbidities that they measure the slightest by transmitted light better than do nephelometers or tyndallmeters by reflected light. The photo-tubes are housed in light, dust and smoke-proof compartments, and when firmly in place need no care at all. In fact, they should not be handled, because moisture from the hands may cause surface leaks (which, however, can be cured by wiping and drying the surface with alcohol). Three of the four photo-tubes in our original instruments are still in operation, one pair for more than three years, and up to now no deterioration or other perceptible change is apparent. Our experience, therefore, supports the theo-

retical assumption that well-made photo-electric tubes are permanent in life and function.

The suspension and magnet of a stock galvanometer, which is truly described as being simple and sturdy, are integral parts of the instrument, and I am grateful to the Leeds and Northrup Company of Philadelphia for providing a special suspension which is abundantly sensitive for the photo-tubes that are the standard equipment of the scopometer. Like the tubes, the galvanometer needs no attention and should not be handled. It does not require leveling, and notwithstanding the wear and tear of three years' continual use and the abuse of repeated transportations in all kinds of vehicles and cutting in and out of many experimental setups, the original galvanometers still function perfectly without ever having needed any kind of attention.

A stock 250 watt projection lamp is the standard light source of the instrument, and when free from defects, these lamps can be changed at will without affecting calibration.

The standard specimen cell has plano-parallel sides 6 millimeters apart and an extended outside edge for convenience in handlingand protection against finger smears. Three cubic centimeters suffice to fill it.

OPERATION

There are two preliminary steps to operating the Photo-Electric Scopometer, i.e., (1) checking galvanometer and (2) setting instrument for the desired determination. (1) To check the galvanometer: switch on the lamp (bridge circuit off) and turn the suspension head of the galvanometer (under the sliding cover in front of the dial) or tilt the instrument to one or another side until the galvanometer rests at zero. (2) To set the instrument for a particular technic: Place the specimen cell holding clear water or any predetermined standard in its recess and set the measuring scale on zero (by turning the button projecting from the right side of the instrument). Then turn on the bridge current and bring the galvanometer back to zero by changing the aperture of the iris or setting diaphragm which is controlled by the fine adjustment in back of the measuring scale.

Both checking and setting are delicate but extremely simple manipulations which need only be done when starting work or changing from one technic to another. However, they take only a moment, and it is well to be sure that the galvanometer registers zero when inactive.

Measurement of unknown samples is exceedingly speedy and convenient. With a specimen in place all one has to do is to turn the button which changes the aperture of the measuring diaphragm until the galvanometer again rests at zero and refer the indicated scale reading to a reference graph or table showing the equivalents of concentrations and scale readings.

The scopometers employ predetermined calibrations in place of the usual standard samples and calculations required in pho-

tometry. This presents no difficulties but rather offers a number of practical advantages such as freedom from troubles and inaccuracies incident to preparation and control of comparison standards, a very considerable increase in speed and convenience of operation, and the ability to measure materials which are too

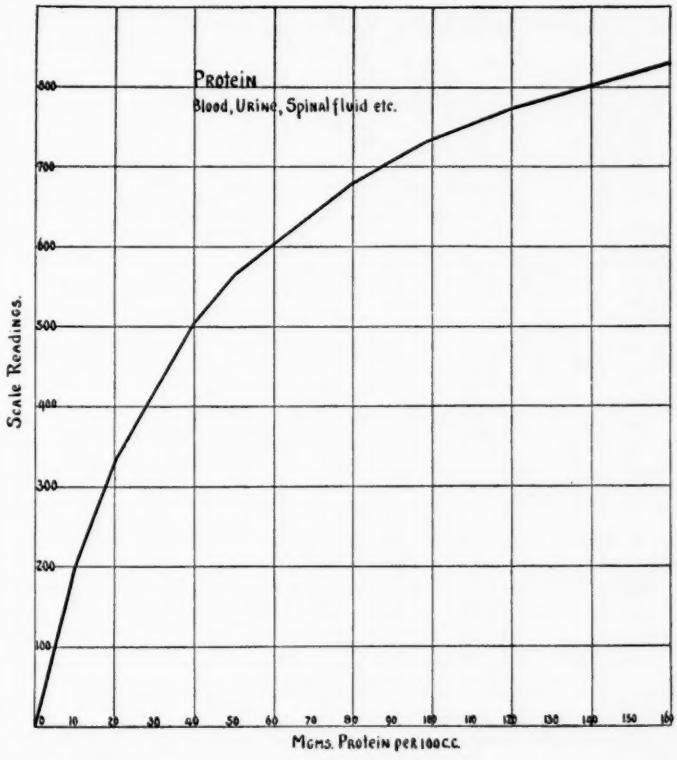

FIG. 3. PROTEIN CALIBRATION OF PHOTO-ELECTRIC SCOPOMETER II

The protein concentrations are plotted against Photo-Electric Scopometer scale readings (Jour. Am. Med. Assn., 80: 529).

scarce or otherwise impracticable for the preparation of comparison standards.

Illustrative calibrations in the form of graphs are shown in figure 3 for protein in blood, urine and spinal fluid, et cetera, in figure 4 for blood sugar by several different methods, and in

figure 5 for hemoglobin by iron and acid hematin methods. A calibration is made by applying any method to a series of known concentrations covering the desired range and plotting the

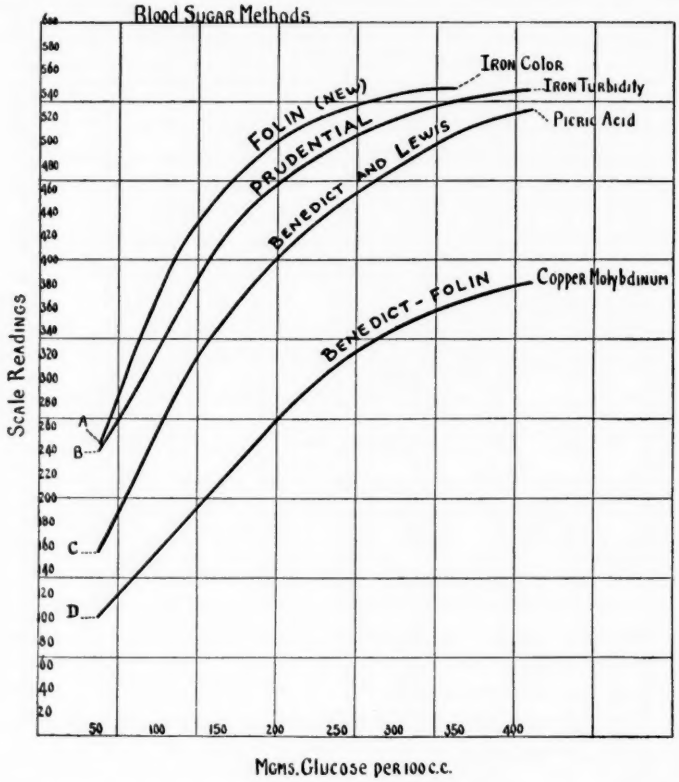

FIG. 4. BLOOD SUGAR CALIBRATIONS OF PHOTO-ELECTRIC SCOPOMETER II BY FIVE DIFFERENT METHODS

Sugar Methods. (A) Blue colloidal suspension (Jour. Biol. Chem., 77: 421). (B) Light yellow turbidity (Trans. Med. Dir. Assn., 1929). (C) Red solutions (Jour. Biol. Chem., 20: 61). (D) Blue solutions (Jour. Biol. Chem., 70: 405; 76: 457).

scopometer scale readings against the concentrations. Thereafter the calibration need never be made again because the scale readings indicated by subsequent similarly treated samples are always referable to the original calibration. Specimens may also

be measured without a pre-determined calibration by adjusting a known standard sample to give the same scopometer reading as the unknown sample. Very critical titrations may similarly be made.

It is, of course, important to measure tests at the right time, which is generally stipulated in the descriptions of methods, but if there is any doubt about the time a reaction takes to reach the

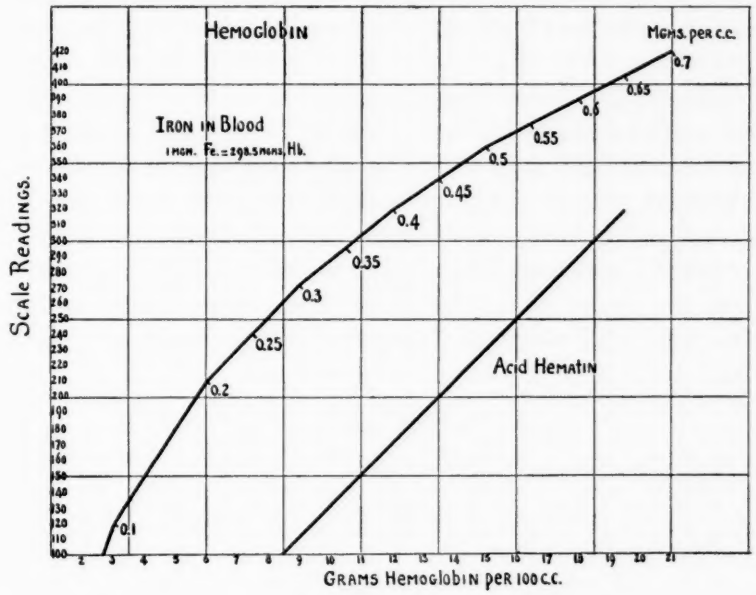

FIG. 5. HEMOGLOBIN CALIBRATIONS OF PHOTO-ELECTRIC SCOPOMETER II

Calibration for the pink and red-brown colors obtained with two different hemoglobin methods.

period of its greatest intensity and stability, it is a simple matter to complete a test on an intermediate concentration and measure it at successive time intervals. In this way crystal and bacterial growth, enzyme action and phenomena like precipitation, agglutination, and lysis may also be measured.

Experiments in measuring the same materials with seven different pairs of similar photo-electric tubes indicate that when the best attainable accuracy is not essential, calibrations will

hold within 5 per cent with different instruments. In the course of an early experiment one of the original tubes was accidentally damaged and another tube substituted for it without apparent effect on calibrations. In another experiment, three novices and an experienced observer measured with the same instrument a series of nine serum protein precipitates running from 10 to 80 mgm. per 100 cc., checking within a quarter of one per cent. Thus, by totally eliminating personal and subjective sources of error the instrument enables the least competent technician to measure as accurately as the most skillful worker.

Chemists and technicians who have used the instrument for experimental and routine work agree that they can measure with it more accurately than they can do the bench work prescribed for determinations. They also emphasize that those who have not had an opportunity to work with the Photo-Electric Scopometer cannot appreciate its ease and speed. Other advantages include the use of micro-samples, extraordinary range and great sensitivity, especially in the lower ranges where sensitivity is most useful.

SUMMARY

A universal self-contained fool-proof instrument which measures the light transmission of macro- and micro-samples photo-electrically in terms of light has been described and the null principles which underlie its remarkably easy and precise operation discussed. A three-year test has proved the sturdiness and reliability of the Photo-Electric Scopometer and demonstrated its superiority over visual methods in range, sensitivity and accuracy.

REFERENCES

(1) Exton, Wm. G.: A new method of colorimetry. Jour. Optic. Soc. Am., **14:** 134. 1927.

(2) Exton, Wm. G.: Scopometry. Arch. Path. and Lab. Med., **5:** 49–65. 1928.

(3) Exton, Wm. G.: The Junior Scopometer. Jour. Am. Med. Assn., **92:** 708–713. 1929.

(4) Exton, Wm. G.: The present status of clinical laboratory measurements with note on photo-electric effect. Am. Jour. Clin. Path., **1:** 237–250. 1931.

EDITORIAL

On the Control of Cancer

'Midst all that is talked, written and done about the control of cancer, there is surprisingly little mentioned of what might be called the ideal of a cure.

Every sympathy is extended to those who must treat the many patients with the disease and appreciation is expressed of the emotions of the patients and their relatives and friends who grasp at every straw in the desperate situation of hopeless cancer. But there must nevertheless be something toward which practising physicians, patients, relatives and in fact every one should look as an ideal sometime to be attained.

When surgery and radiation no longer offer any hope of cure or amelioration and recourse is had to narcotics alone as an easy means of bridging an interval, it might be just as well to again emphasize ideals which should already have been discussed when surgery and radiation were contemplated at the first consultation.

Not that it is not said that "some day, someone will find something;" and even more definitely, "some day someone will find out how to immunize people against it;" or "some kind of chemotherapy will conquer it" and so on.

But what have we on which to base a rational program, on which to plan an ideal?

Some things are known well enough.

(1) All living multicellular organisms increase the number of their cells by a process called cell division.

(2) As the cells increase in number, they are differentiated and organized into the morphology and function characteristic of the species and the parts.

(3) The number, differentiation and organization of cells produced in the majority of species is limited by the organism itself, not only in the total primary cells, but also in those produced

secondarily for repair, regeneration, et cetera. An equilibrium is reached.

(4) In tumors of whatever kind, the number of cells is increased. The equilibrium is disturbed in degrees from slight to complete. Differentiation and organization are diminished in degrees from slight to complete.

(5) There are authentic cases on record in which even malignant tumors have been held in check or have even disappeared through agencies within the organism itself. Many more cases are known, in fact are encountered every day, in which recurrence of tumors has been checked from within for many years after removals which have failed to remove all of the cells.

From these few facts alone, rational plans for future control are obvious. There seems no need to state that when control of inanimate nature is accomplished, it is usually by way of physics and chemistry.

STANLEY P. REIMANN.

NEWS AND NOTICES

Eleventh Annual Convention of the American Society of Clinical Pathologists

May 6 to 9, 1932, New Orleans, Louisiana

The Eleventh annual meeting of the American Society of Clinical Pathologists for the presentation of scientific papers was held in the Jung Hotel, on May 6-7-8-9, 1932. The meeting was attended by fifty members and twenty-seven visitors. The program proved to be of unusual interest to all those present. This program was made notable by an excellent group of papers dealing on the general subject of Hematology and Serology.

The address of the retiring President, Dr. H. J. Corper, was read at the annual banquet and this was followed by an excellent paper on "The Pathology of Amebiasis in Carriers" by Col. Chas. Craig. Greetings from the American College of Surgeons was extended by Dr. M. T. MacEachern and greetings from the American Medical Association were extended by Dr. William D. Cutter.

A feature of the meeting was the dedication of the Department of Pathology, of the Louisiana State Medical School.

The business meeting was called to order at 9:40 A.M., May 9th, by the President, Dr. H. J. Corper.

In addition to the items previously reported in the Journal, the following reports were read and approved. In some instances the report is abridged.

REPORT OF THE SECRETARY-TREASURER

Despite the depression our income from dues this year exceeded the previous year by $320.00. Due to rigid economy in all expenses the income exceeded the total expenses by $114.00, in spite of the fact that the journal costs in excess of one-half of the membership dues. It is obvious that with such a small net income the society must consider carefully any new activity which would call for funds from our treasury. Since the society is now successfully engaged in a

major activity (the publishing of its official journal which has gained for it worthy scientific recognition), it would seem desirable that a certain portion of our cash balance be set aside as a permanent endowment fund for the increase of the scope of the journal. I would suggest that the society at this time set aside $2000.00 from its present assets for this purpose.

The membership is to be congratulated on the fact that approximately 50 per cent of the total dues collected were paid within a month after the bills were sent out. It is only by prompt attention to such seemingly small details that much expense can be saved in handling the affairs of the society.

Your Secretary again wishes to bring to your attention that no member will receive the journal until their dues are paid. As soon as the payment is made, $5.00 of it is sent to the Publisher of the journal. Thus, when dues are allowed to lapse the name is removed from the mailing list of the journal. The reinstatement on the mailing list usually requires sometime and occasionally errors occur as evidenced during this year. Therefore, if you wish to receive your journal without interruption, please pay your dues on receipt of the first statement. If the journal is not received promptly after paying dues, please notify the Secretary.

To date the active membership of the society is 356. Three hundred and six of these have paid the current year dues. Thirty-eight owe for one year and thirteen owe dues for two years. During the past year six members resigned their membership in the society. One of these members resigned for financial reasons, but hopes to be reinstated as soon as his financial condition warrants it. Three members abandoned the field of pathology to engage in the field of internal medicine. Thirteen members were dropped for non-payment of dues and no replies to inquiries could be obtained from them even after the usual registered letter. Eighteen members who owed two years of past dues have now fully paid and are awaiting reinstatement by the Board of Censors. Two members died.

BALANCE SHEET—APRIL 20, 1932 AND STATEMENT OF INCOME & EXPENSE FOR PERIOD FROM MAY 19, 1931 TO APRIL 20, 1932

ASSETS

Balance in bank (Willet, Fink & Wharton Report)		$3,257.17
Investments:		
Commonwealth Edison Company First Mortgage 4 per cent Gold Bond-Par Value $1000.00—Cost		945.00
March 1, 1932 Interest Coupon Attached		20.00
Furniture and fixtures	$601.75	
Less-Reserve for Depreciation	460.86	140.89
Total assets		$4,363.06

NET WORTH

Balance—May 19, 1931			$4,248.82
Income:			
Initiation Fees		$230.10	
Membership Dues		3,710.00	
Interest on Investments		25.33	
Miscellaneous		1.00	
Total		$3,966.43	
Expense:			
Salary	$525.00		
Office Expense	27.70		
Printing and Multigraphing	123.95		
Technicians' Registry	422.00		
Postage	115.00		
Cartage	6.00		
Convention Expense	316.36		
Williams & Wilkins	2,127.91		
Audit	42.50		
Bond	12.50		
Taxes (Colorado)	12.77		
Depreciation on Fixtures	120.35		
Exchange	.35	3,852.19	
Income in excess of expense			114.24
Net worth April 20, 1932			$4,363.06

As you will note the society is in excellent financial conditions, having a cash balance of $3,257.17 and a $1000.00 Commonwealth Edison Bond.

A. S. GIORDANO, *Secretary-treasurer.*

REPORT OF EXECUTIVE COMMITTEE

On recommendation of the Editor of the American Journal of Clinical Pathology, the committee urges that the members give their support, by personal or institutional subscription, to Biological Abstracts.

Recommend that the Society authorize the Secretary-Treasurer to set aside the sum of $2000.00 as a special JOURNAL fund.

Recommend that the Society express its appreciation of the excellent business and editorial management of the JOURNAL by the Editor, Dr. T. B. Magath.

Recommend that an appropriation of $500.00 be made for the expenses of the editor's office.

Recommend that the Society extend to the Publication Committee and to Dr. Kolmer and his co-editors their thanks and appreciation for the excellent character of the book on "Approved Methods of Laboratory Technique."

The committee examined the report and accounts of the Secretary-Treasurer

and found the financial conditions of the society in a highly satisfactory condition, as will be determined in his reports to the Society, and commends the secretary for the excellent and economical administration of this important office.

K. M. LYNCH, *Chairman.*

BOARD OF REGISTRY

We now have a total of 1055 names on our Registry of which 1009 are laboratory technicians and forty-six medical technologists. Two hundred and seventy-one registrants (two hundred and fifty-three laboratory technicians and eighteen medical technologists) were added during the fiscal year and eight names were stricken off the roster.

The growth of the Registry has been quite constant. Hospitals are now demanding our certificates from applicants for positions.

There has been marked improvement in the quality of technicians applying for registration. This has been partly effected by raising the standards of admission in the training schools approved by our Registry which now require a year of college work in chemistry and biology prior to entrance and a minimum period of instruction of twelve months. The members of the Board are making plans for a more rigorous selection of registrants by instituting examinations, oral and written, theoretical and practical.

It is interesting to note that through circularizing our registrants one hundred and nineteen copies of Drs. Kolmer and Boerner's "Approved Laboratory Technic" have been purchased through our registrar.

In a number of the larger cities technicians are beginning to band themselves into local societies for the advancement of their interests. Their aims are chiefly intellectual. At their meetings they have invited clinical pathologists to address them on topics relating to clinical pathology. The registry has encouraged such organizations as they tend to elevate the scientific status of their memberships. Possibly in the not distant future and through their own efforts a national organization of Laboratory Technicians may be effected similar to the one in the nursing profession which will still further enhance the prestige of a calling so essential to the clinical pathologists and so necessary in the human health program.

The Board of Registry has received during the past year a total of $3,877.29 and has expended $2.249.00 leaving a balance on hand of $1.628.29.

PHILIP HILLKOWITZ, *Chairman.*

Report on training schools for technicians

Numerous inquiries have been received in reference to the training of technicians. We have furnished from time to time, a list of the names of the schools for laboratory technicians, approved by the Board, through registration.

The applications of three hospital laboratories were approved, two others and one from a university were provisionally accepted and one rejected during the present session.

Nearly forty schools are now on the list of approved schools, through registration, including several university and college courses in medical technology and the courses offered in hospital laboratories.

We wish to encourage the members of this body who conduct a training course for technicians in their hospital laboratories to have it registered with our Board by meeting the minimum requirements as outlined in our previous report.

Evils of the commercial schools are increasingly too evident to be ignored by the clinical pathologist. It is his duty to counteract these evils by insisting on the minimum standard requirements for the school for technicians and to lend active support to every endeavor to elevate the qualifications of laboratory technicians and the standards of the training schools, through registration with this Board.

KANO IKEDA, *For the Committee.*

REPORT OF THE PLACEMENT BUREAU

The committee wishes to report that during the past year there was received three applications for change of positions and one of these was filled through the help of the bureau.

The committee urges every member that desires a change of location to place his name on file with the committee so that as soon as openings occur the members can immediately be notified.

A. S. GIORDANO, *Chairman.*

REPORT OF THE EDITORIAL COMMITTEE

The American Journal of Clinical Pathology began its second year under very auspicious circumstances. The enclosed letter from the publishers clearly indicates the condition and shows that there is no indebtedness resulting from the first year's activities. This is an unusual showing for it means that we have been able to absorb the initial expenses that ordinarily would take three years to write off. By careful planning, it is obvious that during this year we shall be able to have a more liberal policy concerning the acceptance of illustrations for articles and it may be that the JOURNAL will show a profit.

During the first year the Executive Committee voted to pay for an excess of fifty-two pages but the income from the JOURNAL met this expense and hence it will not have to be borne by the Society. A large number of manuscripts has been submitted to the JOURNAL and these together with other matters had necessitated a considerable amount of correspondence on the part of the editor, resulting in more than one thousand letters being written to transact the business of the JOURNAL.

The JOURNAL is now being abstracted in all of the principle abstracting journals in this country and abroad. It has gained considerable recognition and there is no reason to doubt that the scope of the JOURNAL can be materially increased in the future.

Owing to the good showing during the first year, the publishers have voluntarily agreed to increase the size of the JOURNAL by fifty pages for this year. The number of subscriptions has reached nearly one thousand and when this happens another one hundred pages will be added to the JOURNAL.

Not a small amount of credit for the success of the JOURNAL is due to manufactures advertising in the JOURNAL, and I again urge members of the Society to express their appreciation in whatever way they see fit to our advertisers who in reality have contributed a goodly sum of money to the JOURNAL.

T. B. MAGATH, *Chairman.*

REPORT OF PUBLICATION COMMITTEE

The book on Approved Laboratory Technic has been apparently received in the United States and abroad in a very highly satisfactory manner. A large number of reviews have been published and all have been satisfactory and highly commendatory so that the authors are highly gratified with its reception and particularly since it reflects to the credit of the Society.

The authors also wish to take this opportunity of asking the members of the Society to bring errors to their notice so that these may be corrected in future editions. A reprint of the book appeared early in April and a number of errors were detected in time for correction.

The Committee also wishes to refer with great satisfaction to the success of the American Journal of Clinical Pathology which is largely due to an editor of exceptional ability and a splendid coöperation of the publishers, Williams & Wilkins Company of Baltimore. Indeed we feel that the editorial policy of this JOURNAL has placed it on par with the finest being published and the Society can take great pride in this publication.

JOHN A. KOLMER, *Chairman.*

REPORT OF RESEARCH COMMITTEE

Your committee wishes to report some progress during the year, but regrets that in the assembling of the hematologic registry there has been considerable delay on the part of some of our members in sending in their case reports. About fifteen cases with slides were sent in during the year, most of which were received within the last two weeks. Over an equal number which are of little or no use to the Society were reported without accompanying slides.

Only two men reported their experience with the Friedman test for pregnancy, but as was brought out at the meeting it is hoped that all the members will send in returns on a questionnaire to be sent out soon in order to assemble the data to be tabulated as a commentary to the papers delivered on the subject by Dr. Sondern and Dr. Reinhart.

No data were received in regard to hemoglobin determination according to Osgood and Haskins technique, although fifty-nine men obtained standard

solutions from Dr. Osgood. We trust that we may be able to hear from these men in the near future. We are pleased to report that the Ward Burdick medal was awarded to Dr. Benjamin Kline.

We believe that with participation on the part of our members to a greater degree than in the past, we may be able to assemble information and material available to all members of the Society, which can never be obtained in any other way, and plea for better coöperation with future committees.

A. G. FOORD, *Chairman.*

REPORT OF COMMITTEE ON MEDICAL AND HOSPITAL FUNCTIONS

It was moved and seconded that in view of the difficulties in financing exhibits at medical and hospital associations that this committee be abolished.

C. H. MANLOVE, *Chairman.*

PUBLIC RELATION COMMITTEE

The first meeting of this Society was held with the avowed purpose as stated by the temporary chairman, Dr. Hillkovitz, "to take council how best to strengthen the status of the Clinical Pathologist from both a scientific and an economic standpoint—to analyze our weakness and to institute proper measures for insuring the stability of our specialty, a member of which is unfortunately looked upon as a technician rather than a consultant." With the help of the A. M. A. and other organizations our standing as specialists is now well established. It remains for the individual to advance his field of usefulness and appreciation by physicians, by the brand of work he puts out and by his activities in local and state societies and in hospital staff meetings. Unfortunately however, the same economic problems exist practically unchanged as they did in 1922, namely:

(1) The state laboratory.
(2) Competition of lay hospital laboratories with private laboratories.
(3) Status of approved private clinical laboratories of approved hospital laboratories and approved clinical pathologists.
(4) Competition by technicians.
(5) Relation of the pathologist to the hospital.

THE STATE LABORATORY

There is today unquestionably a drift toward state or socialistic medicine fostered by lay individuals, industrial organizations, insurance companies, and the lay press which seems destined to grow, due in part to the lethargy of the medical profession. The policies of many state board of health laboratories in extending their activities foster and encourage this tendency. Clinical pathologists, who are most seriously affected, because they are, so to speak, in the

front line trenches, should, if they want to continue their existence accept this vanguard position, and individually and collectively resist to the full extent of their ability, this invasion, which will ultimately include the whole medical domain. When the public finds out it can have its laboratory work done at state expense, why should it not look to the same source for its calomel and quinine and its surgery.

One of our members from one state submits evidence in the form of a full page advertisement, of their State Board of Health, in their State Journal which "offers to every Physician Free Laboratory Service of all kinds, offering also free biologicals," and says this pernicious procedure if persisted in will unquestionably stifle all private laboratories in that state.

That the situation is not hopeless can best be answered by citing the results of our endeavors in Indiana, where conditions have been particularly bad. Your chairman in 1928 wrote and had introduced before the House of Delegates a resolution (copy attached to this report), asking the state society to go on record as condemning the socialistic activities of the state board of health, in the following points:

(1) Entering into unfair competition with licensed physicians, making clinical pathology a specialty.

(2) Forcing the expense of private laboratory work on the tax-payers under the guise of Public Health.

(3) That their work should be confined to epidemiology, to indigent patients, and to state institutions. This resolution was referred to the committee on Public Policy and legislation who the following year reported at length (copy of report attached), giving their impressions of the situation. They recommended that the House of Delegates ask the laboratory men of the state to appoint a committee to meet with the state board of health, discuss their problems and report the results back to the House of Delegates. This was adopted and accordingly on August 6, 1930, a committee consisting of Drs. Giordano, Rhamy, Lyons, Langdon, and Forry met with the state board of health. With the backing then, of the state medical society and of the state journal, we succeeded in having them adopt the following proposal:

"That there be printed upon the cards enclosed in Wassermann containers sent out by the state laboratory and requiring the doctor's signature the following statement:

"'This patient is financially unable to pay for this laboratory service and I am making no charge for said service,' also that there be printed upon these cards in bold face type, and requiring the signature of the patient: 'I am financially unable to pay for this laboratory test and I know the state laboratory charges no fee for said laboratory test.' Also upon these cards shall be printed unless the signature of both the physician and the patient appear in proper place, 'this test will not be made by the state laboratory.'"

Supplementary to this understanding an opinion had been obtained from the

Attorney General to the effect that "under the law it was not mandatory that the state laboratory make examination for those who were able to pay, except, and only in case of epidemics, and to preserve community Health."

A report of this meeting and its results was made to the House of Delegates who then officially approved the proposed method. Information cards as agreed upon are now in use in Indiana, as approved by the Indiana State Medical Society (see Indiana State Med. Jour., Oct. 1930). The responsibility of keeping faith now lies squarely on the shoulders of the Secretary of the State Board of Health.

Such a program in every state would go far towards protecting the rights of the Clinical Pathologist. We recommend that the A. S. C. P. officially approve this step on the part of the Indiana State Medical Society and the State Board of Health and by some means urge its acceptance in principle and practice by all state boards.

Therefore the following resolutions are recommended for your approval:

(1) Resolved: That this society express its approval of the action of the Indiana State Medical Association and the State Board of Health of Indiana in requiring that the examinations of their public health laboratories be limited to public institutions and to indigent patients, who must state in writing as well as their attending physician, that they are unable to pay for such laboratory examination.

(2) That a copy of this resolution be sent to the American Medical Association, all state associations and state boards of health, calling attention to these facts and of our approval of the same.

(3) That a copy be sent to all councillors and that they be urged to bring this matter before their state associations and endeavor to have this plan adopted in their respective states.

(4) That full details of this plan be printed in our own Journal for reference.

The arguments used in accomplishing this result in Indiana are as follows:

(1) Extension of the activities of the State Board of Health to all branches of medicine is the road to state medicine.

(2) Encourages unscrupulous physicians to have laboratory work done at state expense, charging the patient and pocketing the fee.

(3) Encourages pauperism on the part of the laymen.

(4) Curtailment of their activities would reduce taxes. Tax-payers should be impressed with the fact that thousands of dollars of state funds are annually diverted for the benefit of private individuals fully able to pay their way.

(5) The value of the community of a fully equipped laboratory in competent hands.

HOSPITAL LABORATORIES

Improvement of laboratory service in hospitals should be encouraged. In many places clinical pathologists have connection with more than one hospital

and this method for the smaller hospitals should be strongly urged by the A. M. A. council.

The present situation as regards standardization of hospitals needs stimulation for betterment. The tendency of lay hospitals to commercialize their laboratory by entering into competition with private laboratories for outside work is wrong in principle.

Although it is realized that in communities where private laboratories are not available, the hospital laboratory must be utilized, yet it should be a cardinal principle that hospital laboratories should not enter into such competition with private laboratories, for by so doing they are invading the domain of medical practice. The clinical pathologist in charge of a hospital laboratory is usually on salary and does not share in fees thus collected, and this amounts to commercializing him at the expense of his fellow pathologists. This competition is most unfair to both the hospital pathologist and the private laboratory, especially when the outside work is done at special hospital prices. This is a growing evil and some remedy should be found. As an instance, one physician in the same office building as your chairman stated he would rather have his work done close at hand if the hospital laboratory prices would be met. Too often the hospital, instead of being a place where physicians take patients for better care and treatment under his order, is in active competition with one or more branches of medicine, and dictate to the physician instead of being subservient to him. It would be a good thing if all laboratories whether private, institutional or public health should be classified and rated. We note that the council of the A. M. A. has "shifted the emphasis in listing from approved laboratories to a more inclusive list of Physicians Specializing in Pathology and allied subjects, whether they are in teaching, hospital, research, governmental or commercial laboratories." Just what the effect of this change will be remains to be seen, but on the surface it seems like a withdrawal of their support of the clinical laboratory. A much more beneficial plan would be to make separate classifications of approved private clinical laboratories, approved hospital laboratories, laboratories for research, et cetera.

TECHNICIANS

Efforts should be continued to have all technicians registered and classified according to their qualifications and to curb their employment in situations not under proper supervision.

B. W. Rhamy, *Chairman.*

REPORT OF NECROPSY COMMITTEE

It is the understanding of this committee that it owes its existence to the unquestionable expression of opinion during the past two years that tissue pathology should receive more prominent consideration in this society in the

future; and it is the belief of this committee that this sentiment is quite universal in the society because it is apparent that the majority of the members, regardless of their hobbies and special interests, are fundamentally pathologists whose daily work includes autopsies and the examination of surgical material.

The one constructive and tangible thing which this committee has to offer is a set of rules which have been formulated dealing with the proper preparation and care of the body after death and during and following autopsy. These rules are designed to eliminate some of the objectionable procedures which have been openly condemned by this society and to institute procedures and precautions which will gain better repute for autopsy work with the laity, the profession in general and the undertakers. These rules, which are at present not type-written, will be submitted to the officers and, it is hoped, the publication committee will see fit to have them published in the official JOURNAL. It is not to be understood that by publishing such rules this committee is attempting to dictate autopsy procedure to pathologists, but they are intended to be used for guidance by professional and lay assistants in the less technical details of routine autopsy work.

(1) This committee believes that any educational campaign or propaganda directed toward the laity had best be handled by the national necropsy committee.

(2) That the chairman of the necropsy committee of this society should automatically be this society's representative on the national necropsy committee.

(3) This committee believes that autopsy demonstration by nationally prominent pathologists should occupy a permanent place on the program of the annual meeting of this society. Such demonstrations could either be scheduled on Sunday or at the time of the meeting of the Executive Committee when the vast majority of the members are at leisure.

O. A. BRINES, *Chairman.*

REPORT OF NECROLOGY COMMITTEE

Whereas we have lost by death two of our members, Dr. W. F. Thompson of Beaumont, Texas and Dr. George Henry Fox of Binghamton, New York

Be it resolved that we express our sincere sympathy to the families of these two departed colleagues.

Obituaries

George Henry Fox was born at Painted Post, New York, in 1882, and received his premedical education at Detroit University and Amherst College. He was a graduate of the University of Michigan Medical School in 1909. He was a past president of the Broome County, New York Medical Society. He died of cerebral hemorrhage on December 26, 1931.

William F. Thompson was a charter member of the American Society of Clinical Pathologists. He was a graduate of Tulane University. For many years he was secretary-treasurer of the State Pathologic Society of Texas.

HARRIET J. LAWRENCE, *Chairman.*

AMENDMENTS TO THE BY-LAWS

The following changes were approved:

Article III, SECTION 1.

Shall be changed to read as follows: All Fellows and Associate Members shall subscribe to this Constitution at the time of their election to membership and shall pay an initiation fee of Ten ($10.00) Dollars, payable with the application for membership.

Article IV, SECTION 6.

Add the following: Whose duty shall be to foster research by Fellows of the Society. They may suggest problems for investigation, foster group investigations, and collect and maintain catalogues of data and materials.

Article V, SECTION 1. At each annual session the Research Committee may designate a Fellow of the Society to receive the Ward Burdick Award. This award shall be in the form of a gold medal which shall be presented to that Fellow who, in the opinion of the Research Committee, has presented the most meritorius contributions to the science of clinical pathology. Rules governing the award shall be made by the Research Committee, approved by the Executive Committee and published for the information of Fellows of the Society. If, in the opinion of the Research Committee, at any annual session no contribution is judged of sufficient merit to receive the award, no award shall be made at that session.

The insertion of the above article as number V automatically changes the number of each subsequent article number.

The incoming President, Dr. Walter M. Simpson moved that the President be given the privilege of appointing the following committees for the coming year: Public Relations Committee, Committee on Local Arrangements, Necrology Committee, Committee on Necropsies.

The motion was voted upon and passed.

The chair of the President was formally turned over to Dr. Walter M. Simpson by Dr. H. J. Corper and being no further business the meeting adjourned at 12:45 P.M.

RESOLUTION PASSED BY THE COUNCIL OF THE MINNESOTA STATE MEDICAL ASSOCIATION, JUNE, 1932

WHEREAS, Both the Radiological Society of North America and the American Society of Clinical Pathologists, through their

respective subsidiary agencies, namely, the American Registry of Radiological Technicians and the Board of Registry of Technicians, are endeavoring to raise and maintain the minimum standards of educational and technical qualifications of technicians in their respective fields, through certification and registration, and

WHEREAS, The American Medical Association, the American College of Surgeons, the American Hospital Association and other responsible national medical organizations have given their unqualified support to this program of certification and registration by the aforementioned Societies, therefore,

Resolved, That the Minnesota State Medical Association, through its Committee on Schools for Laboratory Technicians, extends its hearty coöperation to these Societies in their efforts to elevate the standards of qualifications of medical technicians by recommending to its constituent members and County and District Societies that they urge the clinical laboratory and X-ray technicians under their influence, to identify themselves with the national registry through registration.

Resolved, That the Committee on Schools for Laboratory Technicians of the Minnesota State Medical Society proposes, for the present, at least, to recognize only those institutions which enjoy the approval of the American Society of Clinical Pathologists through registration or recognition and withhold its recognition from all others, pending such registration and approval.

Clinical Pathologists should be familiar with the excellent products manufactured by the Difco Laboratories and the coöperation this firm has shown in developing special bacteriologic mediums. Their laboratories have published a valuable booklet on "Peptones for Bacteriological Culture Media" which contains an accurate analysis of the literature on the subject. It will be sent to members of the A. S. C. P. for the asking.